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ABSTRACT

This monograph was designed for the high school biology curriculum. The first section reviews the major areas of importance in immunology. Section three contains six instructional activities for the high school classroom and the second section contains teacher's materials for those activities. The activities address for students some of the major concepts of immunology. They relate those concepts to lives of students to show how advances in immunology impinge directly or indirectly on their own health, on the health of the community at large, and in the case of Acquired Immune Deficiency Syndrome, on public policy and perceptions of normality. (JD)

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FOREWORD

In 1977 the Task Force on Immunology and Disease of the National Institute of Allergy and Infectious Diseases wrote: "Far from having run its course, immunology presents challenges in the intellectual sphere while promising major advances in the practice of medicine and its specialties."* The intervening decade has borne out the accuracy of that statement as the growth of knowledge in immunology and immunogenetics has substantially improved medical practice. Practical applications of immunology have found increased public attention as organ transplants, the eradication of smallpox, and the rapid rise of acquired immune deficiency syndrome (AIDS) made front-page news. Equally important, the intellectual contributions of immunology and immunogenetics to biology have been remarkable, resulting in improved understanding of issues such as the genetic control of protein synthesis, the role of transposable genetic elements, intercellular communication, and the regulation of the immune response.

As with most such rapidly-moving disciplines, very little of the most recent information in immunology has made its way into the high school curriculum. Indeed, some of that information is so arcane that it is inappropriate for high school students. There are, however, many basic concepts in immunology that illuminate and reinforce the basic concepts that are central to the high school biology curriculum, concepts such as diversity and the complementarity of structure and function.

The Biological Sciences Curriculum Study and the Foundation for Blood Research undertook development of this monograph to bring both the new information and the basic concepts to the attention of teachers and students. We believe we have identified and explicated, with the help of an excellent advisory committee and writing team, the major areas of importance in immunology. You will find those reviewed in the six chapters that constitute section I. Section III contains six instructional activities for the high school classroom. (Section II contains the teacher's materials for those activities.) We have attempted in the activities to address for students some of the major concepts outlined for you in section I. In so doing, we have also tried, where possible, to relate those concepts to the lives of students, to show them how advances in immunology impinge directly or indirectly on their own health, on the health of the community at large, and in the case of AIDS, on public policy and perceptions of normality.

We are grateful to the National Science Foundation and the American Association of Immunologists for their support of this project. We hope you enjoy using the materials as much as we enjoyed developing them. We welcome your comments and suggestions for improvement.

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*U.S. Department of Health, Education, and Welfare. *Immunology: Its Role in Health and Disease.* DHEW Publication No. (NIH)77-940, 1977.

David, the "bubble boy" (Figure 1.1), was born without an immune system. What would happen to him without his bubble?

Heart transplants are common now, but only because of the development of drugs that suppress rejection of foreign tissue. What would happen if the drugs were stopped? Why is an artificial heart not destroyed by the immune system while a transplanted human heart is?

A developing fetus is foreign tissue, yet most pregnancies end with the successful delivery of a healthy baby. Why does the immune system reject a transplanted organ but not a developing fetus?

AIDS is a frightening disease whose incidence is increasing exponentially. The public is alarmed, and state and local governments pass regulations to restrict the activities of AIDS patients. Fear and misinformation abound. What is AIDS? What does the virus that causes it do to the immune system?

It is spring and there is pollen everywhere. Your head hurts, you sneeze, you sniffle. You feel miserable . . . in short, you have hay fever.

While visiting a farm, you trip and fall over an old, rusty rake that the farmer uses to clean out the barn. Because you have a bad puncture wound from the rake, you visit your physician, who wants to know when you last had a tetanus shot.

All those situations involve the immune system. Most simply, the immune system keeps us from getting sick and helps us to survive in a germ-infested world. When we do get sick, the immune system helps us recover. The immune system recognizes and destroys foreign substances such as bacteria, viruses, fungi, and transplanted organs. Without an immune system, we face rapid and certain death from the multitude of germs in our environment.

Figure 1-1. David, the "bubble boy," was born with combined immune deficiency syndrome. He had to live in a sterile environment to prevent infection and disease. (From "Emerging from the Bubble," *Time* 123(8):72, 10 February 1984. Courtesy Associated Press.)

Nonspecific immunity prevents infection.

The main job of the immune system is to prevent infection in the first place. Skin is one of the best protections against the dirty world we inhabit. As long as our skin is intact, no pathogens can enter and cause disease by that route. The gastrointestinal (GI) tract has many ways to prevent entry of organisms into the body proper and confine them to the GI tract. Saliva and tears contain lysozyme, an enzyme that destroys many bacteria. Cilia line the trachea and sweep organisms into the acidic environment of the stomach (pH=2.0) where many of them are killed.

The gut is filled with bacteria, most of which are helpful, or at least not harmful. Their presence prevents harmful organisms from attaching to the gut wall and multiplying. If the harmful organisms can reproduce only in the lumen of the gut, they can be swept from the body by normal peristaltic action. The mucus membranes that line the walls of the trachea and lungs trap many organisms and prevent them from entering the cells. Organisms that remain within the hollow organs such as the gut or uterus do not induce immune responses unless they attach to the walls of the tissues, damage the tissues, or enter the tissues through tiny lesions.

Those are all part of *nonspecific immunity,* so called because they nonspecifically prevent any germs from entering the body, regardless of whether they are helpful or harmful. The exceptions are small molecules such as digested food, water, or drugs.

Infection versus disease.

If there is a break in the protective barrier, such as a cut in the skin, or if there is such an overwhelming number of bacteria that not all of them are killed by the saliva or stomach acid, then we become infected. Infection means that the bacteria, viruses, fungi, or parasites have taken up residence in the body, in a site where they do not belong.

Infection is not the same as disease. Disease occurs when there is tissue damage or impaired function, as evidenced by signs or symptoms. With infection, the cells and serum proteins that make up the immune system come into play. There are phagocytes, leukocytes (white blood cells) that ingest and kill organisms and cell debris in many organs of the body including the skin and the liver.

HISTORICAL INSIGHTS

Humans long have been familiar with the concept of immunity. The ancient Greeks realized that people who had recovered from deadly plagues would never again contract that disease. The English physician Edward Jenner was one of the early pioneers in manipulating the immune system. He developed smallpox vaccination, and his story is an interesting example of observation and experimentation. Louis Pasteur put vaccination and immunology on a scientific basis with the development of immunization procedures for anthrax and rabies.

The late nineteenth and early twentieth centuries were times of rapid growth in the fields of microbiology and immunology, as scientists and physicians came to accept the germ theory of disease. Some of the greatest scientists of the time debated whether immunity resided in the cells or in the "humors" (plasma) of the blood. Of course, both groups were correct; modern research has demonstrated how the two major components of the immune system—cellular and humoral—work interdependently.

Perhaps the greatest achievement of immunology has been the global eradication of smallpox, once the greatest scourge of humankind. Smallpox has been eliminated through the successful immunization of millions of people.

Many of these phagocytes act nonspecifically, that is, they will ingest almost anything that is not normally found in the body. The most important mediators of nonspecific immunity are *neutrophils* and *macrophages*, both of which are phagocytic cells. Those cells are critical in controlling the growth of pathogens (disease-causing organisms) until specific immunity can be generated. By far the most important cells in controlling bacterial infection are neutrophils, because, unlike macrophages, they are extremely efficient phagocytes even in the absence of serum factors. Macrophages, however, are critical in stimulating other cells in the immune system.

Proteins in the blood—antibodies produced by lymphocytes—will bind to the invading pathogens. Together with other blood proteins or with macrophages, antibodies kill or incapacitate the pathogens. Specific killer cells may appear; those are lymphocytes that can help destroy cells infected by viruses, even without an antibody. Usually, the immune system is successful, and the invading organisms are destroyed before they are able to cause disease.

The immune system helps us recover from disease.

Sometimes the immune system loses the battle, and we become ill. The immune system then has the additional task of helping the body recover from disease. The immune system moves into high gear; lymphocytes multiply and differentiate, and large amounts of antibody are produced. Antibody binds to the pathogens and, with the help of serum proteins and macrophages, destroys them. Other killer cells arrive to help destroy viruses.

A sick person often develops a fever, which can slow down the growth of the pathogen and may even destroy it. Frequently, the immune system is able to mount a large enough response fast enough that the infection is brought under control, and the patient recovers. If the pathogens are bacteria, the physician will administer an antibiotic such as penicillin. That drug does not kill bacteria, but rather prevents them from dividing. So, while the immune response is increasing, the number of bacteria is staying the same, and the immune system ultimately is able to destroy all of the bacteria. Fortunately, with the assistance of the immune system, we are able to recover from most infectious diseases.

Sometimes, however, the immune response is not successful and the patient dies. That may occur because the infection was so large that the body was badly damaged before the immune system could destroy the pathogens. Sometimes it is because the infected site is so critical to life—the brain, for example—that even a little damage can cause death. Sometimes the immune system does not work properly, either because not enough of the right kind of antibody is made, or because the specialized cells of the immune system do not function properly. Most of the time, however, the patient recovers.

Recovery from infection leads to long-lasting immunity.

Recovery from an infection usually leads to protection against reinfection by that particular organism. The immune system has memory; that is, the second time it encounters an invading organism, the system responds very quickly, and the pathogens are completely destroyed before they have time to establish an infection, much less cause disease. However, recovery from one infection usually has little effect on immunity to another organism.

With some diseases, the immunologic memory is irrelevant, because of the persistence of antibodies produced during the initial infection. That is the reason for lifelong immunity to certain childhood diseases.

Although infection and recovery from disease effectively immunize an individual and prevent reinfection, some diseases are so serious that it is better not to have them at all. For those diseases, immunization is the better method of acquiring immunity. For example, recovery from polio leads to lifelong immunity, but the consequences of polio can be severe. Even if the individual does not die of the disease, he or she is often paralyzed partially or totally. Polio vaccine, however, effectively immunizes an individual with minimal risk.

Summary

The primary role of the immune system is to prevent infection. However, when that is unsuccessful, the immune system becomes involved in the body's recovery from infection and disease. Recovery from disease leads to long-lasting immunity.

2. CHARACTERISTICS OF THE IMMUNE SYSTEM

The immune system can respond to an enormous number of different antigens.

When faced with an invading microorganism, the immune system responds by destroying the invader. However, almost anything can induce an immune response, including many things other than microbes. An *antigen* is any substance that stimulates a specific immune response. The immune system is capable of recognizing and responding to at least a hundred million (10^8) different antigens. Antigens are usually proteins, carbohydrates, or glycoproteins; fats and inert substances such as carbon particles are generally not antigenic. A single microorganism, even one as small as a virus, has a large number of antigens on its surface, and the immune system is capable of responding to each of them.

The immune response is specific.

The functions of the immune system are carried out by various cells or molecules. The most important molecules are *antibodies*. These glycoproteins (proteins with carbohydrates attached to them) are produced by certain lymphocytes called *B cells*. The cells include the killer cells, some of which can kill only with the help of antibody, and others that function independent of antibody.

The immune system responds to an antigen by generating antibodies and cells that will react specifically to that antigen. Those antibodies and cells will bind only to the molecular structure of that antigen, or one that is very similar, and to nothing else. Thus, the immune response to tetanus is specific for tetanus and will not protect against polio.

One of the reasons you can have many colds over a lifetime is that there are hundreds of different cold viruses, and you mount an immune response to only one of them at a time. When you are exposed to another cold virus, therefore, you can become infected with that different virus, and get another cold. On the other hand, there is only one kind of chickenpox virus, so when you have had that disease, you will never get it again.

Flu is a different story. The flu virus has an unusual genetic structure, and every 10 years or so the virus undergoes major genetic changes. Those changes lead to changes in the surface antigens of the virus, which induce immune responses. So, although you are immune to the flu you had last year, you will not be immune to a new variant of the flu that may arise next year. You, therefore, once again come down with the flu.

The immune response has memory.

Once you have been immunized against tetanus, for example, you will not contract the disease, because the immune response has memory. The second (or subsequent) time the immune system encounters an antigen, the immune response will be larger and will occur more rapidly than the first time. A secondary response can be effective as early as three days after infection, whereas a primary immune response takes approximately seven days to become effective.

Antibodies are produced in response to antigen.

There are two major components to the immune system: humoral and cellular. *Humoral immunity* is provided by antibodies, which circulate in the serum portion of blood and in the lymph. *Cellular immunity*—or cell-mediated immunity—as the name implies, involves certain cells of the immune system such as phagocytes. The activities of those two components of the immune system are interdependent and complementary.

Antibody molecules are bifunctional, binding to antigen with one end and to *effector* cells and proteins with the other. (Effectors are cells or protein molecules that carry out the functions of the immune system.) The *Fab region* (fragment antigen-binding) binds specifically to antigen. Each antibody molecule has two identical antigen-binding regions. There are as many Fab regions as there are antigens.

The other end of the molecule, the *Fc region* (fragment crystalizable), binds to specific receptors on effector cells or on other plasma proteins. Those will then destroy antigen. There are only five kinds of Fc regions, one for each of the five classes of antibodies.

The structure of the antibody molecule allows the immune system to cope with an almost infinite variety of antigens, using only a few different effector mechanisms.

The structure of an antibody leads to its dual function.

Antibody has two functions: to bind to antigen and to bind to effector cells and plasma proteins. The effectors provide the biologic activity that enables the immune system to inactivate or destroy antigens. The function of antibody, as in all other biologic systems, is directly related to its structure. An antibody molecule (Figure 2-1) is made up of four polypeptide chains connected to each other by disulfide bonds. Two of the chains are fairly small and are called light chains; the other two are larger and are called the heavy chains. One light chain is connected to one heavy chain in the amino terminal half of the heavy chain. This pocket formed by the combination of one light chain to half of one heavy chain is the Fab region. The carboxyl terminal portions of the heavy chains are connected to each other, forming the Fc region.

There are two kinds of light chains and five kinds of heavy chains. The five classes of antibody molecules—IgM, IgG, IgA, IgE, and IgD—correspond to the five

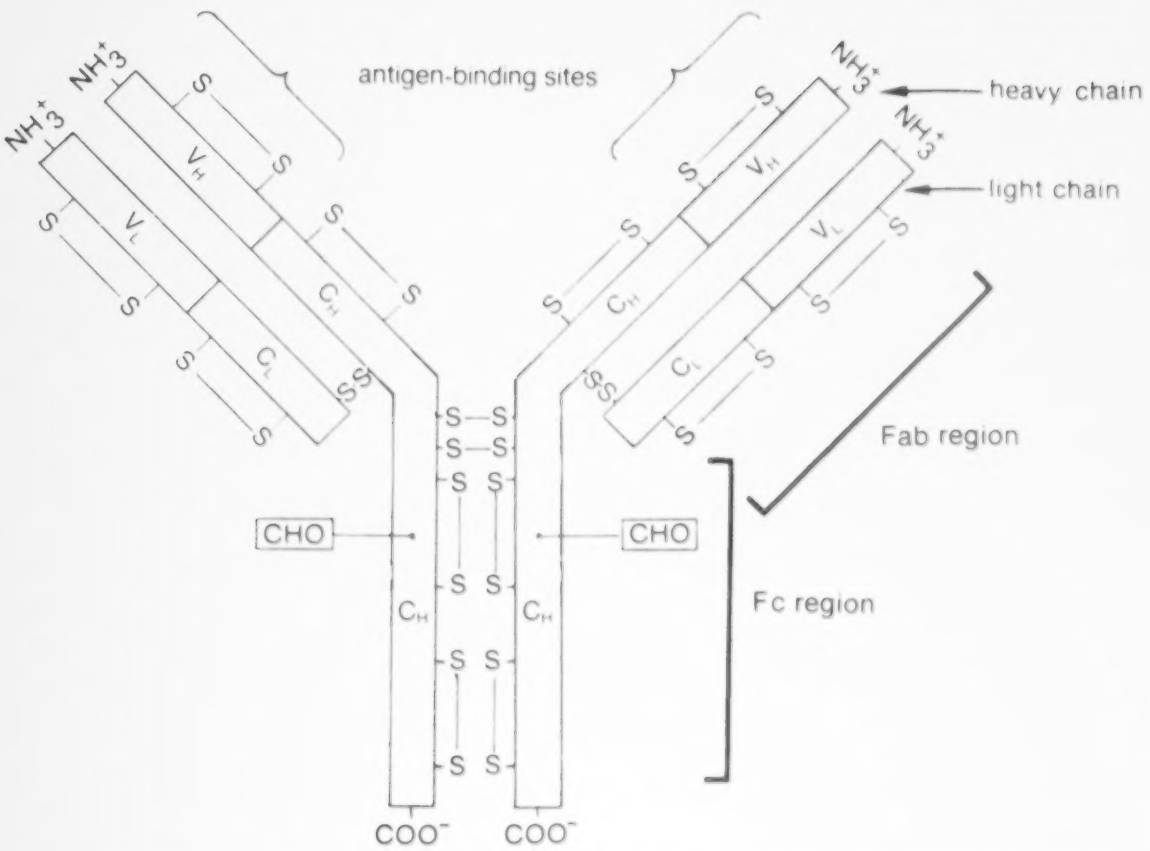


Figure 2-1. Schematic diagram of an immunoglobulin molecule, showing the joining of the heavy (H) and light (L) chains to form two identical antigen-binding sites (Fabs), which contain the variable (V_H and V_L) regions of the heavy and light chains. The two heavy chains are joined in the constant (C_H) regions to form the Fc region. The chains are joined to each other through intra-chain disulfide bridges (S-S); there are also inter-chain disulfide bridges, which cause the molecule to fold. CHO represents the attachment of carbohydrates. (From Hood, et al., *Immunology*, 2nd ed., Addison-Wesley Publishing Company, 1984.)

kinds of heavy chains. IgM, shown in Figure 2-2, is unusual because it contains five of these four-chain units.

The amino acid sequences of the carboxyl terminal ends are nearly identical among all chains of a given kind, and hence are called the constant regions. In contrast, the amino terminal ends are very different and, therefore, are called the variable regions. Thus, the constant regions of all IgM antibodies are identical, but their variable regions are very different. The molecular structure of the antibody leads directly to its dual function, because the Fab region resides in the variable portions of the molecule, and the Fc region in the constant portions.

Antibody diversity is genetically controlled.

The enormous diversity of antibody specificities derives directly from the variable regions. However, uncovering the mechanisms that generate this diversity has been one of the more difficult problems of modern immunology.

The immune system can make about 10^8 antibodies, each with a different specificity. If each of those antibodies is

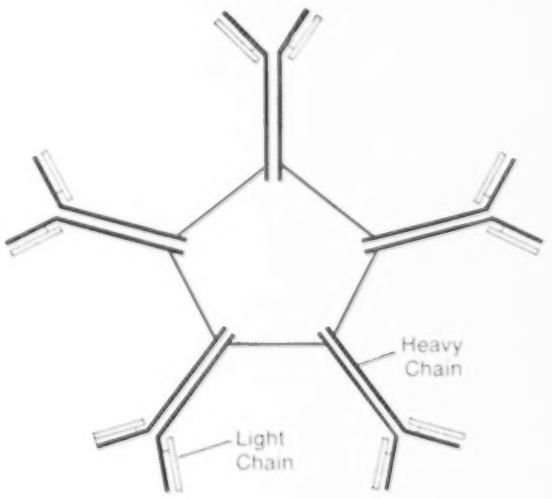


Figure 2-2. Structure of the IgM antibody molecule. (BSCS, 1986.)

encoded by a different gene, the amount of DNA that must be used to produce all those different antibodies would be enormous. (Some authorities calculate it to be approximately two percent of all available DNA.) Assume, however, that any heavy chain can combine with any light chain. If heavy chains are encoded by one set of genes, and light chains by another set, then a person needs only 10^4 light chain genes and 10^4 heavy chain genes to make 10^8 antibodies. Furthermore, if variable regions are encoded by genes different from those that code for constant regions, then the number of genes necessary drops further.

During the 1970s, scientists developed methods for isolating specific genes, cloning them, studying their structure, and determining their frequency in the genome. Consequently, they were able to study the sequence of the DNA and the transcribed RNA and compare that to the known amino acid sequence of the antibody molecule. This led to one of the most exciting discoveries in the area of molecular genetics, namely that a single polypeptide chain for an antibody is not encoded by a single locus on the DNA molecule. Rather, bits and pieces of the gene are scattered about, and are separated by intervening sequences of DNA that do not appear to code for anything.

Furthermore, as the organism develops from a gamete to a multicellular adult with many kinds of differentiated cells, the genome undergoes tremendous rearrangement, including excision of parts of the DNA, and movement of genes from one part of the DNA to another. It is now apparent that during this process of genetic rearrangement, certain components must be assembled into a functioning genetic locus (Figure 2-3). The selection and assembly of these components proceed in "Chinese menu" fashion, that is, one locus from column A, one from column B, and so on, until the entire locus is assembled. Such a mechanism of gene rearrangement leads readily to a very large number of different antibodies without the necessity of equally large numbers of genes.

Antibodies work with cells or serum proteins (complement) to destroy antigens.

When stimulated by antigens, the immune response produces many different antibodies with many different specificities. Sometimes, just by binding to the antigens on the surface of the pathogen, the antibody can render the pathogen nonpathogenic, thereby preventing disease. For example, when antibody binds to a toxin, which is a protein molecule about the same size as an antibody molecule, the toxin is unable to bind to or damage a cell. Likewise, when antibody binds to certain antigens on the surface of a flu virus, the virus cannot attach to and enter a cell and cause disease.

Antibodies are very small when compared to microorganisms (Figure 2-4), and most of the time just binding to an antigen on a microbe has no effect. Other components of the immune system must actually destroy the antigen. The two most important effectors of antibody-dependent immunity are macrophages and complement.

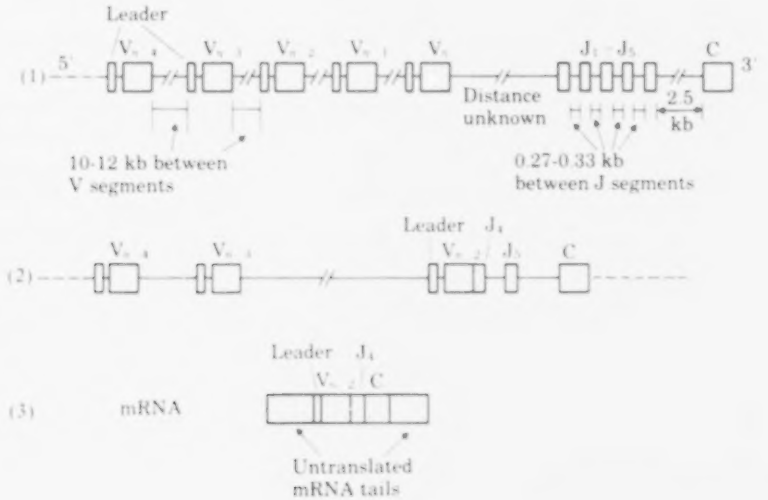
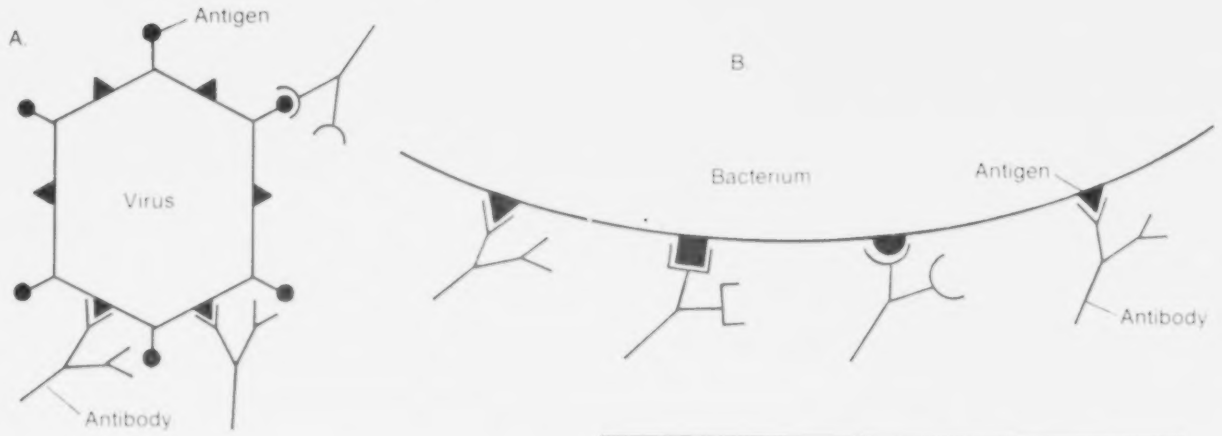


Figure 2-3. Genetic rearrangements for making a light chain. The boxes represent genes, and the connecting lines are intervening DNA sequences. (1) The DNA of an immature B cell has many L (for "leader sequence") + V + J (for "joining sequence") and C genes for a light chain separated from each other. (2) During maturation, one L + V gene and one J gene are brought near each other by chopping out the intervening DNA. Note, however, that the L + V genes to the left and the J genes to the right of the rearranged gene are still present. Those variable region genes are still separated from the C (constant region) genes. The entire complex is transcribed into RNA. (3) The intervening sequences are excised from the RNA; all three genes are now continuous. This RNA makes the final functional light chain. Except for the number of genes involved, the genetic rearrangements are similar for the assembly of a heavy chain. (From Alfred Nisonoff, *Introduction to Molecular Immunology*, Sinauer Associates, Inc., 1982.)



Relative Sizes

	diameter	volume
protein (antibody)	1	1
virus	10	10^3
bacterium	100	10^6
B cell	1000	10^9

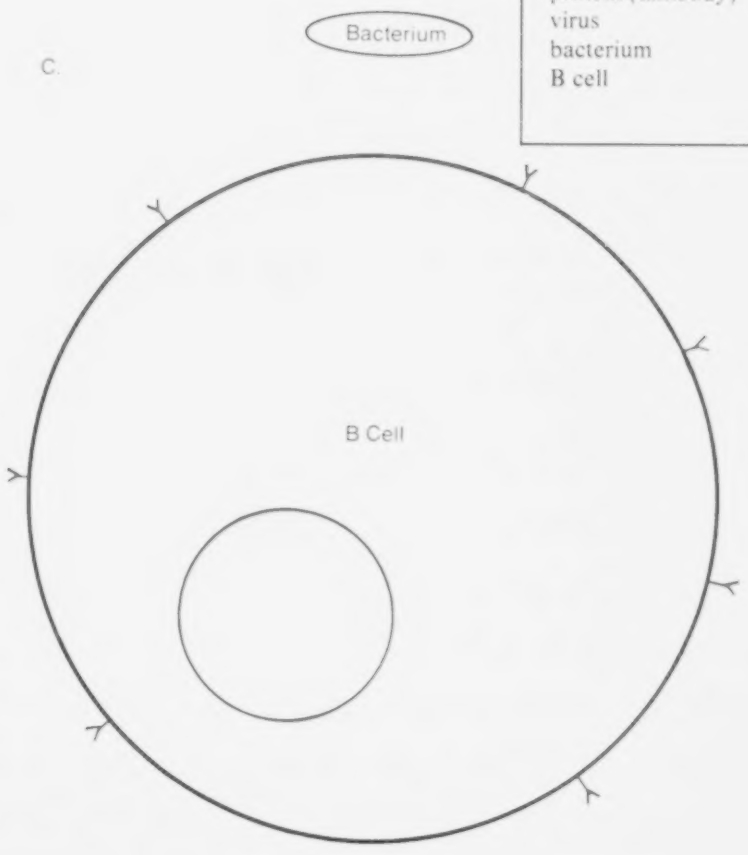


Figure 2-4. Highly schematic representation of antibodies binding to (A) a virus and (B) a bacterium. A B cell is beside a bacterium in (C). Drawn approximately to scale. (BSCS, 1986.)

Macrophages are phagocytic cells that exist in the circulation and are found in many tissues such as the skin and liver. They have receptors on their surfaces that will bind to the Fc portion of an IgG or IgM antibody. When a macrophage encounters a bacterium that is coated with IgG or IgM antibody, it is able to phagocytose (ingest) the bacterium. Through the use of enzymes and oxygen products, such as H_2O_2, it then kills the bacterium. Macrophages kill antibody-coated organisms very efficiently.

Other cells, mainly certain kinds of lymphocytes, are also able to kill antibody-coated organisms. Unlike phagocytic cells, they kill the target cell without ingesting it. The mechanism of destruction is not known, but it does require that the killer cell bind antibody to its surface via the Fc region, and that the killer and target cell come into contact with each other.

A very important effector of antibody-dependent immunity is *complement*, a group of proteins found in the serum. When antibody binds to antigen, the complement

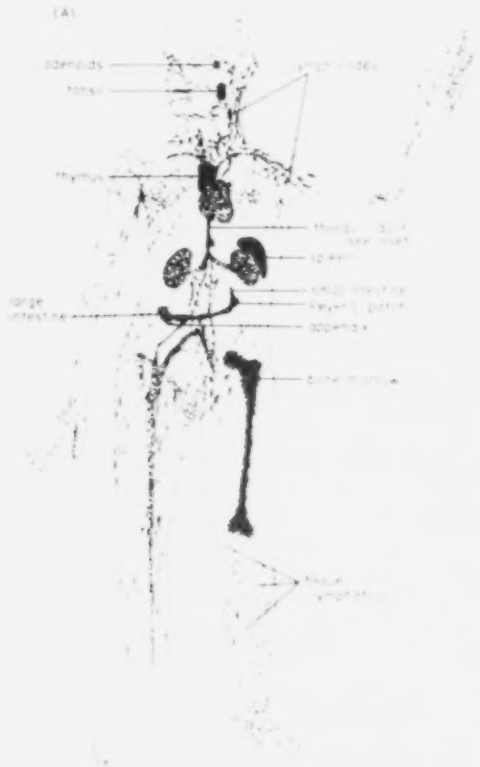
THE IMMUNE SYSTEM CONTAINS BOTH FIXED AND CIRCULATING CELLS

Because antigens can enter any part of the body and can be found anywhere, the immune system must contain cells that can move throughout the body. There are also fixed tissues where the cells grow and develop. Further, because a few invading organisms might avoid the circulating cells and antibodies, there are also effectors, both cells and antibodies, in many other tissues (see Figure 2-5).

Leukocytes, including macrophages and lymphocytes, all come from hemapoietic (blood-producing) tissues of the bone marrow. Some lymphocytes undergo a period of development in the thymus; those cells become the T cells. After their development, T cells move from the thymus into the circulation and the lymphatic vessels, and into organs such as the spleen and lymph nodes. They are also found in other tissues, particularly in the tissues of the intestines and the tonsils.

Other lymphocytes never go to the thymus; these are the B cells, the cells that produce antibody. They also are found in circulation and in the major lymphoid organs, the spleen and the lymph nodes, as well as in other tissues. Likewise, the macrophages are found both in circulation and in tissues.

During an infection, leukocytes move from the blood to the sites of infection and return to the circulation via the lymphatic vessels. The spleen and lymph nodes serve an important role in filtering antigens from the blood and concentrating them in a region containing many lymphocytes. The liver, which is frequently overlooked as an immune organ, contains many macrophages, and is a major organ involved in the destruction of bacteria and other antibody-coated microbes that gain access to the blood.



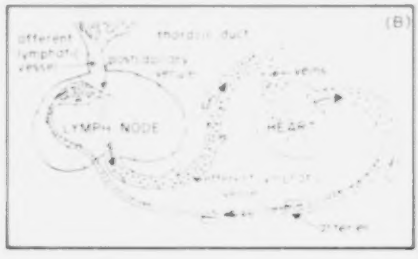


Figure 2-5. The human immune system with the major organs in black. The cells are produced by the bone marrow of the long bones and mature in thymus (T cells) or spleen (B cells). Lymphocytes and antibodies return to the blood from the tissues and lymph nodes by way of the lymphatic vessels. The lymphatic vessels join the circulatory system at the thoracic duct (inset). (From Joklik, et al., *Zinsser Microbiology*, 18th ed., Appleton-Century-Crofts, 1984. (A) Adapted from Jerne, "The Immune System," *Scientific American* 229:52, July 1973. (B) Adapted from Gowans, *Hospital Practice* 3:34, 1968.)

proteins are activated and bind first to the antibody and subsequently to the antigen. Once they have bound to the antigen, complement proteins can mediate the destruction of antigen in two ways.

First, as shown in Figure 2-6, complement can literally poke holes in the cell wall and cell membrane of bacteria and parasites. Once that osmotic barrier has been breached, the cell pops.

The second mechanism by which complement destroys cells involves macrophages. The activated complement proteins attract macrophages to the antigens. Furthermore, macrophages have receptors on their cell membranes that will bind activated complement and enable macrophages to engulf and destroy antigens that are coated with complement. One should remember that unactivated complement has no biologic activity, and that complement is activated by antibodies that have bound to antigen. Those controls are critical to prevent the complement system from destroying all the cells in the body.

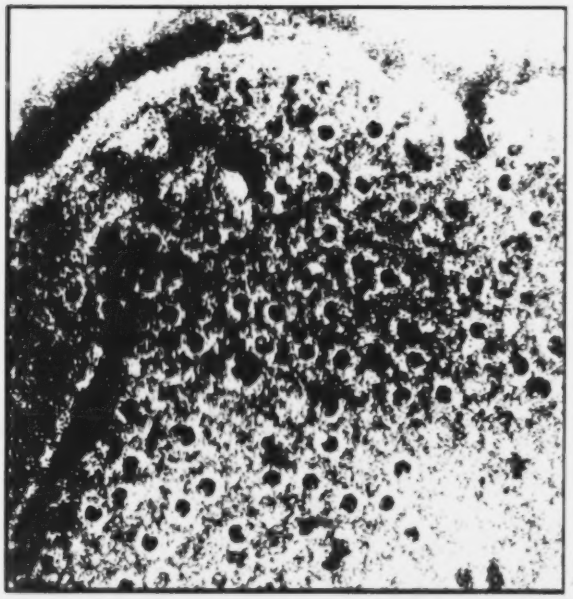


Figure 2-6. Complement induces lesions (holes) in the plasma membrane of a cell ×400,000. (From Clark, *The Experimental Foundation of Modern Immunology*, John Wiley & Sons, 1980. Adapted from J. Humphrey and R. Dourmashkin, "The Lesions in Cell Membranes Caused by Complement," *Advances in Immunology* 11:75, Academic Press, Inc., 1969.)

Immune responses also generate effector cells.

Although antibody, either alone or in conjunction with macrophages, lymphocytes, or complement, can kill many organisms, there are certain pathogens it cannot destroy. For example, antibodies can inactivate viruses and prevent them from entering a cell, but once a virus has entered the cell it is safe from antibody. For that type of infection, the immune system has another weapon, the cytotoxic T cell.

A *T cell* is a lymphocyte that matures in the thymus, hence its name. There are several different kinds of T cells. Most are involved in regulating immune responses by controlling their magnitude and nature. However, the particular role of cytotoxic T cells is to kill foreign cells, particularly virus-infected cells.

A cell that contains viruses often has viral antigens on its surface. The cytotoxic T cell recognizes those foreign antigens on the cell surface, and kills that cell. Again, the mechanism of destruction is not yet known, but the cytotoxic T cell must come in contact with its target.

Another role for cytotoxic T cells is the destruction of transplanted tissue. The cytotoxic T cells recognize these foreign cells and destroy them, in a manner similar to that by which they destroy virus-infected cells.

This ability of cells, particularly macrophages and T cells, to respond to foreign antigens, to regulate the responses of other cells in the immune response, and to destroy antigens without the assistance of antibody is known as *cell-mediated immunity*.

Summary

The immune system, which is composed of fixed and circulating cells, is capable of responding to an enormous variety of antigens. The immune response is specific: the products of immune-system activation—antibody and cytotoxic cells—will react only with the antigens that stimulated the response and with no others. The immune system also has memory, so that the second, and any subsequent, time the system encounters that same antigen, the response is much faster and larger than it was in the first encounter.

Antibodies are glycoproteins produced by lymphocytes—B cells—following stimulation by antigen. Antibodies have regions that bind to antigens and regions that bind to effector molecules such as cell receptors and serum complement. Although the number of different antibody-binding configurations is extremely large, there are only five different configurations for binding effectors. Such a system allows antibody molecules to recognize and bind to a large number of different antigens but requires only a few common effector mechanisms to destroy the antigen.

The great diversity of antigen-binding regions is encoded in the DNA of the B cell. During development of the organism and maturation of the B cell, the DNA undergoes complex rearrangements, and by a random assortment of various genetic loci into one functional unit, the lymphocytes are able to make a huge number of different antibodies using only a few hundred genes.

Antibodies provide resistance to infection either alone or in conjunction with other effectors. With a few exceptions, the binding of antibody to antigen does not, by itself, result in the destruction of that antigen. Usually, antibody-coated organisms are destroyed by phagocytic cells such as macrophages, by killer lymphocytes, or by the soluble serum proteins of the complement system. Furthermore, not all antigens can be destroyed by antibody, and cell-mediated immunity is required to eliminate certain organisms such as intracellular viruses.

3. INITIATION AND REGULATION OF NORMAL IMMUNE RESPONSES

What happens the first time: a primary response.

Although B cells produce antibody, the induction of an antibody response requires the interaction of three kinds of cells: B cells, macrophages, and helper T cells. The development of those cells from stem cells in the bone marrow is shown in Figure 3-1.

Like cytotoxic T cells, helper T cells mature in the thymus. They are regulatory cells that enhance immune responses and ensure that the immune response is directed against foreign antigens, not against self.

B cells have antibodies in their membranes, with the antigen-binding region (Fab) facing out and the Fc region imbedded in the membrane. To produce and secrete antibody, B cells must receive two signals (Figure 3-2). The first signal occurs when antigen binds to the Fab region of the membrane-bound antibody. The second signal is a soluble protein made by helper T cells. Except in rare instances, the B cell must receive both of those signals simultaneously to become activated, divide, and secrete antibody.

Helper T cells respond to antigen only when they encounter it on the surface of a macrophage (Figure 3-2). Moreover, that macrophage must have on its surface certain antigens that the T cell recognizes as "self." Thus, in order for a helper T cell to become activated and send the helper signal to B cells, it must encounter antigen + self; *antigen alone does not work.*

The macrophage, which is a phagocytic cell, engulfs the antigen and displays it on the surface of the macrophage. If

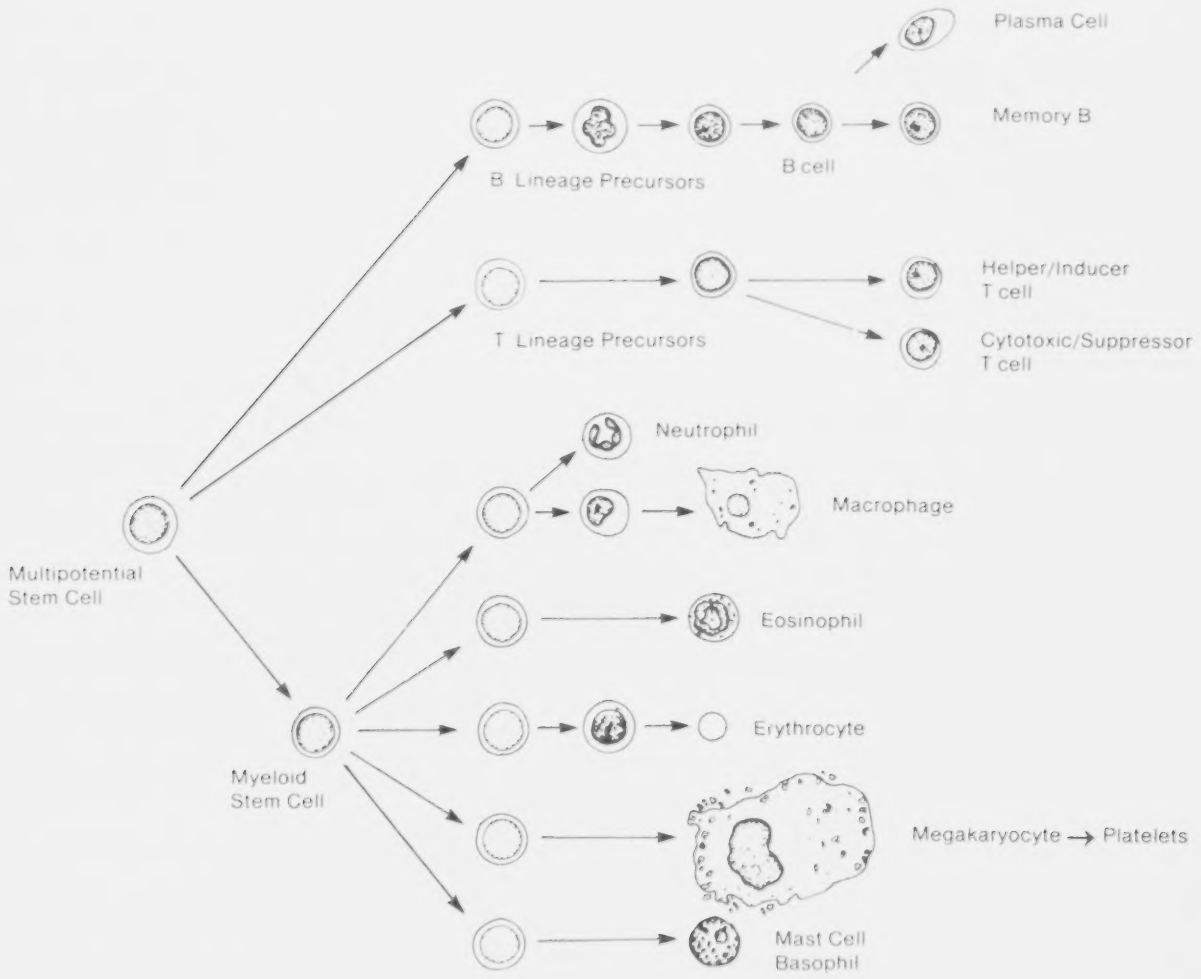


Figure 3-1. Maturation of blood cells from common precursor cells. The development of cells in the myeloid pathway takes place in the bone marrow, whereas the development of the lymphocytes takes place either in the thymus (T cells) or in various lymphoid organs, especially the spleen (B cells). Each differentiation pathway requires different controlling hormones and stimuli. (From Hood, et al., *Immunology*, 2nd ed., Addison-Wesley Publishing Company, 1984. Courtesy Paul W. Kincade, PhD.)

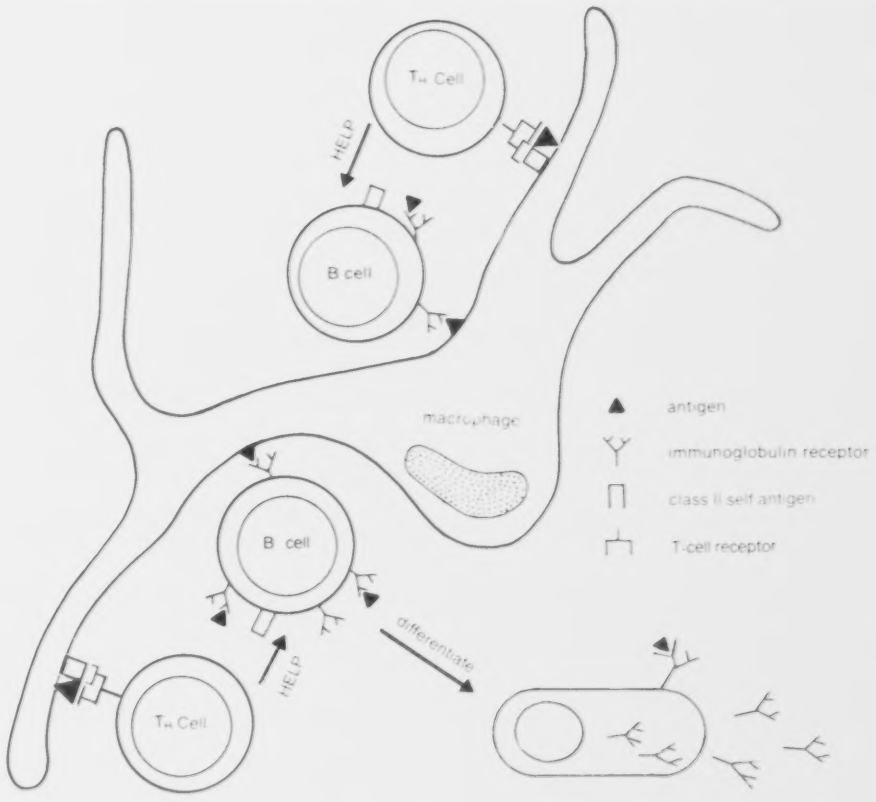


Figure 3-2. Interaction of antigen with macrophages, B cells, and helper T cells (T_H cell) leading to the production of antibody. (From Hood, et al., *Immunology*, 2nd ed., Addison-Wesley Publishing Company, 1984.)

the macrophage has self molecules, the T cell will recognize this self + foreign antigen complex, become activated, divide, and produce the helper factors needed by the B cells.

For example, when tetanus antigen is injected into the body, it is engulfed by a macrophage. The macrophage processes the antigen, and displays the antigen on its surface as a tetanus + self complex. This complex is recognized by a helper T cell that is specific for tetanus, but which responds to tetanus only as an antigen + self complex. The T cell then secretes factors that activate B cells. To become activated and secrete anti-tetanus antibodies, B cells must simultaneously bind helper factors and tetanus antigen.

Likewise, the generation of cytotoxic T cells in a primary immune response requires the simultaneous interaction of macrophages, foreign antigen, helper T cells, and the cytotoxic T cell. With the help of factors secreted by the helper cell, the cytotoxic T cell divides and differentiates, and is thus able to kill cells that have specific foreign antigens on their surface. Cytotoxic T cells that destroy virus-infected cells must recognize viral antigen + self molecules, and will kill only cells with that complex. Therefore, cytotoxic T cells specific for hepatitis virus will not be able to kill cells infected with hepatitis virus when transferred into an unrelated individual. Table 3-1 shows the interaction between effector cells and helper cells.

The secondary response.

During the primary immune response, the specific T and B cells increase in number. When the response ends, there are more of those antigen-specific cells than there were initially. A second encounter with the same antigen proceeds in a manner very much like the primary response. The important difference now is the number of antigen-specific T and B cells.

EFFECTOR CELLS	HELPER CELLS	OUTCOME
B cells	helper T + macrophages	antibody
cytotoxic T cells	helper T + macrophages	cell killing
macrophages	helper T	phagocytosis & cell killing

Table 3-1. Interaction between effector cells and helper cells. (BSCS, 1986.)

In a person who has not encountered a particular antigen, there are very few cells that can bind that antigen. During the primary response, the number of antigen-binding cells increases exponentially, as much as 10-10,000 fold. During a secondary response, therefore, the number of cells responding is very high. As a result, the amount of helper factor and the number of antibodies increase very quickly. Figure 3-3 demonstrates the difference in antibody concentrations in primary and secondary responses.

A secondary response by cytotoxic T cells is similar. Although the same types of cell interactions must occur in both primary and secondary responses, the secondary response is much faster because there are more specific helper and cytotoxic T cells present.

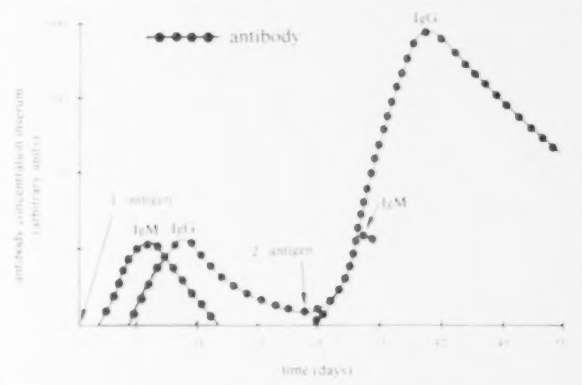


Figure 3-3. The appearance of IgM and IgG in the serum during a primary and secondary immune response. (Adapted from Hood, et al., *Immunology*, 2nd ed., Addison-Wesley Publishing Company, 1984.)

MEASURING ANTIBODY LEVELS

The amount of antibody in the serum can be measured in a number of ways. If the antigens are on the surface of an organism, such as a bacterium, the ability of the antibody to destroy the bacteria can be used as a measure of antibody concentration. The greater the amount of antibody in the serum, the more the serum can be diluted before losing the ability to destroy bacteria. For antigens on the surface of cells, including bacteria and erythrocytes, antibody levels can be measured by agglutination. If there is a high concentration of antibody, one Fab region can bind to an antigen on one red cell, while the other Fab region of that same antibody molecule can bind to the antigen on another red cell. The cells will then be linked, and if that happens between many antibodies and many cellular antigens, the cells will clump, or agglutinate. Agglutination is the method used in blood typing.

Antibody levels can also be measured by more sophisticated means that require special reagents and detection devices. A widely-used example is the ELISA test. In that test, antigens are fixed to a plastic surface, and the test serum is added. After allowing time for the antibodies in the serum to react with the antigens on the plastic, the unbound serum is washed away. A second antibody is added. This antibody is specific for human immunoglobulins and will bind to any antibodies that might have bound to the antigen. Those second antibodies have been chemically coupled to an enzyme. After allowing the binding to occur, and washing away unbound antibody, the substrate for the enzyme is added, and the production of the end-product is measured, usually by using an enzyme-substrate system that produces a colored end-product. One simply measures the amount of color produced by the reaction. The result obtained from using the test serum can be compared with the results obtained from using a serum that is known to contain antibody. An ELISA test is used widely to screen donor blood for antibody to the AIDS virus.

T cells distinguish self from nonself.

The immune system has a complex task. Not only must it recognize and destroy all foreign antigens, it must also destroy *only* foreign antigens. The immune system, therefore, must be able to distinguish between self and nonself.

T cells discriminate between self and nonself. They do that by means of *histocompatibility antigens*. Histocompatibility, or self, antigens are similar to blood-group antigens. There are two major groups of these self antigens, and they differ in tissue distribution and function. One group, class I, is on all cells in the body except erythrocytes and is responsible for rejection of tissue grafts.

When the immune system destroys a transplanted liver or kidney, it is recognizing as foreign these particular class I antigens. Furthermore, the self molecules that cytotoxic T cells must encounter in conjunction with viral antigens are class I antigens. In humans, there are at least three genes, each having up to 40 alleles (alternate forms), that encode those antigens. Thus, each person has his or her own, extremely rare, combination of class I self antigens. T cells are nonresponsive to class I self antigens, and they cannot be activated by the class I antigens of the individual in whom they matured.

T cells, B cells, and some macrophages have a second type of self antigen on their surface, the class II antigens. Those self antigens are found only on cells of the immune system and not on other cells in the body. Class II self antigens are responsible for controlling the ability of helper T cells to respond. Helper T cells cannot respond to class I self antigens because they have been made tolerant, perhaps by exposure to the antigen in fetal or early postnatal life. Hence, they cannot help B cells make antibodies against normal self tissues, nor can they help cytotoxic T cells kill self. They can respond to foreign antigen in association with class II self antigens, and that usually occurs on the surface of a macrophage.

Helper T cells, then, can only be activated by self (class II) + antigen. That complex normally occurs only on the

surface of macrophages that have processed antigen. Therefore, helper T cells are responsible for preventing the accidental destruction of the body by the immune system. Moreover, since they can respond only to self (class II) + antigen, they are not distracted from their job by any antigens that may be in the circulation, but that are not on the surface of a macrophage.

HISTOCOMPATIBILITY ANTIGENS INDUCE GRAFT REJECTION

The self antigens that enable T cells to distinguish self from nonself are responsible for graft rejection. In humans, these antigens are known as HLA (human leukocyte antigens). HLA antigens were discovered originally during attempts to transplant tissues between unrelated individuals. Since transplants were successful only between "compatible" individuals, these antigens were called histocompatibility antigens. The class I antigens are called A, B, and C, each coded for by a different gene that has hundreds of alleles (each allele is given a number). Successful tissue transplants require both the donor and the recipient to have identical HLA-A, HLA-B, and HLA-C. Because HLA antigens are inherited linked in classical Mendelian fashion, transplants between related individuals have a higher chance of success than do transplants between unrelated individuals. Class II antigens in humans are called HLA-D. Those are antigens recognized by helper T cells in association with foreign antigens.

Genes within the HLA complex are also related to the ability to make immune responses to certain antigens and to the incidence of certain diseases. For example, people with sensitivity to wheat gluten, a condition known as celiac disease, frequently have HLA-A1 and HLA-B8. The reasons for that disease association are unknown. In recent years, researchers have discovered a number of other associations between particular diseases and particular HLA types.

Immune responses are turned off.

When antigen is no longer present in the system, the immune response to that antigen must be stopped so that the body does not use its energy and proteins to make unnecessary antibodies and effector cells. Several mechanisms to accomplish this are depicted in Figure 3-4 and explained below.

1. Antibodies are removed from circulation. Those that have bound antigen will be removed by the various effector systems, especially cellular receptors. Unbound antibody is broken down to amino acids (as are many other proteins) as part of normal homeostasis and the recycling of molecules. Furthermore, all cells in the body have a finite life span, and the activated cells that produce such components as antibody and helper factors will eventually die.

2. A second important factor in terminating the immune response is the loss of antigen from the body. Antigen bound to antibody is filtered out by various organs, and the antigen is either degraded intracellularly by phagocytes or broken down by various enzymes, especially those in the liver.

If no antigen is present, no more cells will be activated, and the immune response will not keep increasing. However, the loss of antigen will not deactivate cells that have been activated to produce helper factors or antibody, or to mediate cytotoxicity.

3. Antibody itself acts as a feedback regulator. The mechanism for that regulation is not known precisely, but the presence of specific antibody somehow interferes with the further formation of antibody.

4. Suppressor T cells play an extremely important role in turning off immune responses. Like the other T cells, these lymphocytes mature in the thymus, but instead of helping initiate immune responses, they turn them off. Experimental evidence suggests that helper T cells are activated first and suppressor T cells are activated later, perhaps days later.

Suppressor T cells probably act by suppressing the activity of helper T cells and thus preventing the generation of help that the B cells and cytotoxic T cells need. There is also evidence that suppressor T cells can suppress B cells directly. Thus, suppressor T cells can turn off ongoing immune responses. Suppressor T cells appear to act through soluble factors, just as helper T cells do. Suppressor and helper factors, however, are different from each other.

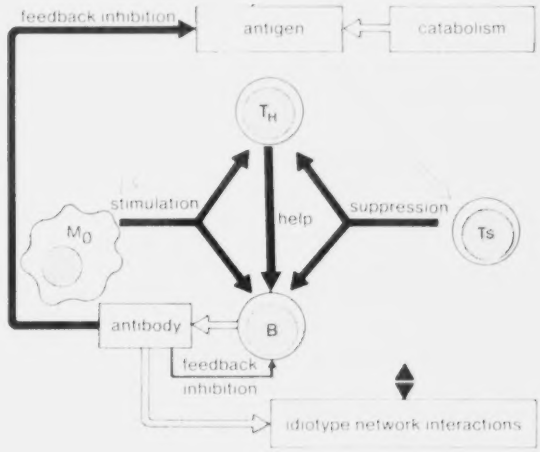


Figure 3-4. Regulation of an antibody response by helper T cells (T_H), suppressor T cells (Ts), and antibody. (From Roitt, et al., *Immunology*, Gower Medical Publishing, Ltd., London, 1985.)

THE NETWORK HYPOTHESIS: A NOBEL PRIZE FOR RESEARCH ON REGULATION

Another regulatory role of antibody is called the network hypothesis, for which Niels Jerne (pronounced YER-nee) won the Nobel Prize in 1984. The Fab portion of an antibody is different from any other structure in the body. It can, therefore, itself be recognized as foreign and can induce an immune response. Furthermore, the most antigenic parts of an antibody are those molecular structures within the Fab region that distinguish it from all other Fab regions, the *idiotype*.

An antibody that reacts against an idiotype is called an anti-idiotype. An anti-idiotype is itself an antibody, with an idiotype, which can induce the formation of an anti-idiotype, which would, therefore, be an anti-(anti-idiotype). An anti-(anti-idiotype) is itself another antibody, which induces the formation of an anti-idiotype, which of course, would be an anti-[anti-(anti-idiotype)], which of course, is an antibody, which induces . . . and so on.

Potentially, the entire immune system could be involved in making antibodies against antibodies, and not against foreign, potentially lethal, antigens. Anti-idiotypes bind to an antibody, and because they bind to the Fab region, they can inhibit the binding of antigen. Such an inhibition of antigen binding may inhibit cell function.

The relationship between idiotypes and anti-idiotypes is shown in Figure 3-5. If a particular antigen is shaped like a box, then the Fab region of that antibody (call it an antibox antibody) will be shaped like the reciprocal of a box, an open rectangle. At least some of the anti-idiotypes against that antibox antibody will fit into this open rectangle and will, therefore, look like a box. An anti-idiotype against this antibody will once again look like an open rectangle.

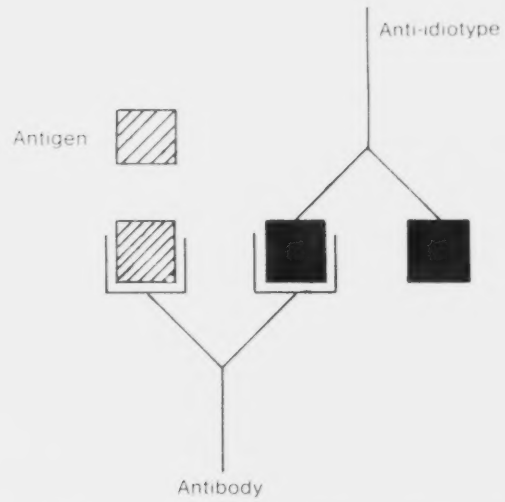


Figure 3-5. Interactions of antibody, antigen, and anti-idiotype. An antibody against the anti-idiotype (an anti-[anti-idiotype]) would look like the original antibody. (BSCS, 1986.)

The predictions of the Jerne hypothesis are: (1) an antibody, with its idiotype, will bind to antigen; (2) an anti-idiotype will bind to the antibody, but not to the original antigen; (3) and anti-(anti-idiotype) will bind to the original antigen, but not to the first antibody; and (4) an anti-[anti-(anti-idiotype)] will bind to the first antibody but not to the original antigen.

Experimental evidence supports that idea. We do not yet know why the immune system does not spend all of its energy making anti-idiotypes.

The immune system responds to the internal environment.

Like the other organ systems in the body, the immune system is part of the whole, and factors that affect one part of the body can affect the entire body. Two important examples are nutrition and stress.

Poor nutrition can affect the immune response. The effectors of immunity are either cells or plasma proteins, so a diet deficient in proteins will render the individual unable to make the necessary products for cell division and protein synthesis. Many cell functions require vitamins, and vitamin deficiency can certainly influence immune function. (There is, however, no evidence that massive doses of any vitamin—doses significantly larger than those needed for normal functioning—have any beneficial effect on immunity, including immunity to colds and tumors.) Certain minerals are needed for proper cell and membrane function. In short, any dietary imbalance that affects cell function and protein formation will have a negative effect on the immune system.

Stress is a potent immune suppressor. Stress acts through the endocrine system to induce production of corticosteroids by the adrenal glands. Those hormones severely suppress the immune system and are capable of killing lymphocytes, particularly T cells. Consequently, a person under stress is frequently more susceptible to infections than a relaxed individual. A good example of that is herpes virus infection. Herpes simplex virus infects nerves of the mouth and face. Most of us carry the virus and usually have no signs of infection. However, under stress, the immune system is suppressed, particularly the T cells, and the herpes viruses, which normally are sequestered in nerve cells, escape immune control and cause fever blisters and cold sores. When the stress decreases, the sores heal because the immune system is able to bring the viruses under control again.

The endocrine system has a potent influence on immunity, and immune responses are affected not only by products of the adrenal glands but also by sex hormones, and probably by most other hormones.

Not surprisingly, the circulatory system is closely linked to the immune system, because the effector cells and molecules of the immune response are in the blood and lymph. The proteins involved in blood clotting are related to the proteins of the complement system, and some substances, particularly bacterial products, can activate the complement system in the absence of antibody.

Summary

The generation of an immune response requires the interaction of T cells, B cells, and macrophages. B cells that have bound antigens to their surface antibodies are activated to produce and secrete antibodies following stimulation by a soluble factor produced by helper T cells.

Helper T cells are stimulated to produce that factor only when they encounter antigen as a complex of foreign antigen + self molecules (class II). The complex is formed on the surface of macrophages. During the primary immune response, the number of cells capable of recognizing antigen expands exponentially. As a result, subsequent encounters with the same antigen produce a much faster immune response, because there are many more responsive cells present.

An important role of the immune system is to discriminate self and nonself; that is accomplished primarily by T cells. All cells in the body, except erythrocytes, have class I antigens on their surfaces; T cells do not respond to those antigens. Cells of the immune system express another kind of self antigen, class II. When the T cell encounters a foreign antigen in the presence of class II antigens, the T cell is activated and provides the necessary stimuli for activating other cells of the immune system.

Once antigen has been eliminated from the body, the immune response must be turned off. Antibody is removed from circulation either by receptors for Fc regions on various cells or by catabolism. The cells that secrete the various products, including antibody and helper factors, are turned off or die. The cells can be turned off by feedback mechanisms that involve antibody. The most important "stop" signal comes from another T cell, the suppressor T cell, which turns off helper T cells and probably B cells, as well.

Like the other systems in the body, the immune system is affected by the environment. Poor nutrition and stress are important suppressors of effective immunity.

4. PROTECTING THE INDIVIDUAL

Natural exposure to an infectious organism may result in one of several outcomes: (1) no obvious infection, with no specific immunity established (uninfected); (2) no obvious disease, but with immunity established to that organism and its products (a subclinical infection); (3) frank disease that subsides with therapy or time and that causes no induction of specific immunity; (4) disease that subsides with therapy or time and that induces immunity; or (5) overwhelming disease and death.

Several factors influence the consequences of infection, including the general health of the individual, the environment, the individual's genetic constitution, and the nature of the pathogen (and any of its toxic by-products). For many infectious diseases, the physician can intervene and manipulate the immune response for the benefit of individuals at risk. Most persons have experienced active immunization from a very early age, but it is also possible to protect or treat a nonimmune individual with passive immunization. For example, an individual exposed to a life-threatening infectious disease such as tetanus, and who has no pre-existing immunity to that organism, may be treated with suitable antibodies made in other individuals. Antibodies may also be produced in other animal species. For example, snake bites can be treated with antiserum produced in horses. Such products must be used with great caution in humans, however. Finally, it is now possible to treat individuals who have an abnormally low immune response with substances that stimulate both lymphocyte division and their functional activity.

Passive immunization.

The transfer of immune serum or cells to a nonimmune individual is known as *passive immunity*. For example, it is possible to protect nonimmune individuals with passive antibodies to the tetanus toxin (the antigen) produced by *Clostriduim tetani*. This is the "T" in the common DPT shot. In the earliest studies and applications, antibodies to either tetanus or diphtheria toxins were produced in other species, commonly the horse, by immunization with a nonlethal, chemically-modified toxin, or *toxoid*.

Patients treated in that manner recovered from the bacterial disease, but one in 20 developed a severe, sometimes fatal, reaction to the foreign horse serum proteins 10 days to two weeks after the treatment. This serum sickness was characterized by fever and chills, muscle and joint pain, and general malaise. This is one reason that passive immunization that employs antibodies produced in other species is used infrequently. Such therapy is used if it is the only life-saving course of action and if the patient has no prior history of passive immunization.

The undesirable effects of passive immunization can be circumvented with the use of human antibodies produced in volunteers. Passive immunization with human antibodies has been effective against measles, mumps, pertussis (whooping cough), tetanus, and hepatitis type A. Unfortunately, animal antibodies must still be used in the treatment of diphtheria, botulism, rabies, and venomous snake bites.

If there is no history of vaccination, passive immunization may be required to save the life of the patient. In that case, passive immunization is usually coupled with *active immunization* (see below) to provide both immediate relief and long-lasting protection. For example, a patient who has an open, contaminated wound and no history of tetanus immunization should be given human anti-tetanus antibodies in one arm for immediate protection and be immunized with tetanus toxoid in the other arm.

Tetanus infection is one example where natural exposure, that is, infection, leads to disease but does not induce immunity. The concentration of toxin sufficient to cause disease and possibly death is below that necessary to immunize. Therefore, active immunizations with tetanus toxoid are required.

Passive immunization with antibody is also used to protect certain individuals who have a particular *immunodeficiency disease*. A small number of individuals are born with a defect in their capacity to make antibodies. In contrast, their cell-mediated immune system is intact and functional. Those individuals have a characteristic pattern of recurring infections with pathogenic bacteria. Some patients benefit greatly from regular injections of human antibodies.

One of the side effects of passive immunization is that the host's immune response to antigen may be suppressed. That phenomenon occurs naturally in the human fetus and newborn. Before birth the human fetus is capable of producing an immune response; however, the fetus also derives from the mother, through the placenta, antibodies that help prevent infection in utero. After birth, the maternal antibodies persist in the infant's circulation for a significant period (Figure 4-1). Immunization, if done too early, would

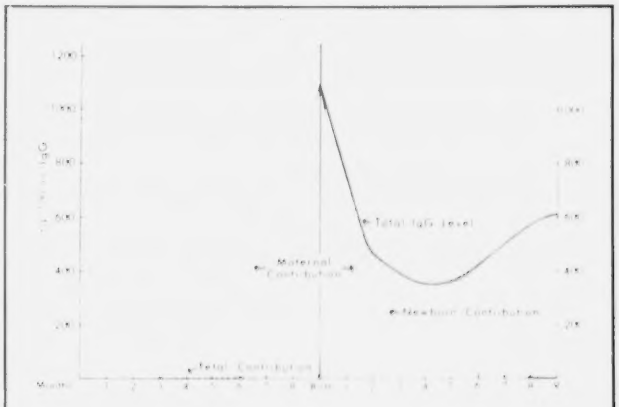


Figure 4-1. Schematic representation of IgG concentrations in the fetus and newborn. (From Faulkner, ed., *Human Development*, W. B. Saunders Company, 1966. Adapted from Jerne, "The Immune System," *Scientific American* 229:52, July 1973.)

be ineffective, because the maternal antibodies would destroy the antigen in the vaccine before the boby's immune system could respond to the presence of the antigen. Therefore, immunization is usually delayed a few months to a year depending on the nature of the vaccine. If the newborn is being breast-fed, he or she is also protected with antibodies in the mother's milk.

These observations have been used with remarkable success in the prevention of Rh disease (or hemolytic disease of the newborn). Rh disease occurs as a blood group incompatibility between the mother and the fetus. If the mother is Rh negative (lacks the red blood cell Rh antigen) and the fetus is Rh positive (expresses the red blood cell Rh antigen), the mother may become immunized against this antigen at the time of birth. At that time a small amount of fetal blood may leak into the mother's circulation as the placenta is delivered. There is no risk to the first child, but subsequent pregnancies with Rh+ fetuses stimulate an immediate immune response in the mother. These anti-Rh antibodies can cross the placenta and bind to the fetal red cells. This complex of antibodies and red cell antigens stimulates an accessory system to destroy fetal red blood cells. The result may be fatal.

This disease can be prevented if the genetic disparity between father (Rh+, dominant) and mother (Rh-) is identified, and the mother is treated with a large dose of human anti-Rh antibodies, *RHOGAM*, at the time her first child is delivered. The treatment is more than 98 percent effective in suppressing the maternal immune response to Rh+ red blood cells. The few failures are thought to be due to unsuspected pregnancies, such as early miscarriages, or to unreported prior pregnancies.

In summary, passive immunization, despite its limitations, is useful in providing immediate relief and protection during that critical time when the individual is at most risk to the consequences of infection or toxin activity and is not yet capable of mounting a significant immune response. The effectiveness of the antibodies will depend upon their relative concentration, antibody class, affinity for the antigen, and their biological half-life in circulation. Because these antibodies have a finite biological half-life, their effectiveness is only temporary, and follow-up active immunization is generally recommended. In addition, because antibodies may also suppress the host's immune response, the timing and route of subsequent active immunization may be very important variables.

Active immunity.

The phenomenon of immunity has been recognized for thousands of years. For example, survivors of an epidemic were immune to reinfection, and they could safely minister to those still ill. More than 20 centuries ago the Chinese had developed a means of specific protection to smallpox based on the use of dried material from smallpox pustules to induce a milder form of the disease. The treatment resulted in significantly reduced mortality, and the practice was adapted and spread widely through the Middle East by Arab traders.

Edward Jenner, an eighteenth century English physician, noticed that milkmaids who contracted a mild form of cowpox disease were immune to smallpox. Jenner hypothesized that immunization with material from cowpox lesions might be used to induce immunity to the much more virulent smallpox. His results were spectacular, and, indeed, in the nineteenth century Pasteur coined the term vaccination from the Latin word vacca (cow) in honor of Jenner's contributions.

Pasteur and his contemporaries did recognize this relationship and used it to develop and refine the technique of vaccination as a means of preventing disease. Pasteur developed a series of vaccines from cultures of pathogenic bacteria that had been treated to reduce their virulence while maintaining their antigenic nature. Thus, the vaccines could be used safely to induce immunity to the more virulent forms of the pathogenic organism. Vaccine development progressed at a rapid pace for the next 50 years until the advent of *antibiotics* in the early twentieth century. Antibiotics, produced by microorganisms, have the ability to inhibit the growth of other microorganisms. The best-known example is penicillin.

BARRIERS TO THE DEVELOPMENT OF VACCINES

One reason vaccines are not available for more pathogens is that many are very complex organisms. Bacteria, for example, are very complex antigens; they express several distinct antigens that theoretically could be recognized by the immune system. Unfortunately, many of those bacterial antigens induce only a weak, short-lived immune response. Only recently have researchers been able to isolate and purify many of these bacterial antigens using new techniques in molecular biology, and the expectation is that better vaccines will be available in the next two decades.

A second reason for the slow development of bacterial vaccines has been the development and widespread use of antibiotics. Many people believe that use of antibiotics such as penicillin, tetracycline, and erythromycin is sufficient to control and treat all bacterial infections. That is not true. Some bacteria are resistant to the antibiotics. In other instances, genetically-resistant variants in populations that are generally susceptible to treatment will proliferate. The result is a new population that is resistant to treatment, a good example of evolution and natural selection.

There is now a resurgence in vaccine development, which has benefited from new technologies in molecular biology that allow the isolation and cloning of genes that encode specific protein antigens. These cloned gene products should be a source of highly purified and inexpensive vaccines (see chapter 6).

The major advantages of active immunization by vaccination over immunity by natural exposure are the greatly-reduced risk of overwhelming disease and death, the predictability of response, and control over when and how immunity is induced in individuals.

Although laboratory techniques now allow the immunologist to assess the type and magnitude of the immune response following vaccination, the ultimate test of immunity is demonstrated resistance to the specific disease. Vaccines, therefore, undergo extensive testing during development for the degree of protection they afford, the length of immunity conferred, and any undesirable side effects. In general, there are now good vaccines for many viruses, several bacterial toxins, and few bacteria.

Because infections represent the largest group of illnesses, they are the most frequent problem facing physicians and account for the greatest share of medical costs. In addition, these diseases have an impact in loss of income and productivity that is measured in billions of dollars.

Vaccination has had a dramatic effect on several diseases and thus on both economic and social factors. Figure 4-2 shows the effect on poliomyelitis in response to vaccination in the United States. The reduction in incidence represents a 1,000-fold drop in this disabling and very expensive disease.

Under the auspices of the World Health Organization (WHO), worldwide vaccination against smallpox has resulted in confirmed eradication of the smallpox virus and the disease. The impact of that achievement is impossible to assess, but urban life as we know it could not exist if smallpox were still endemic.

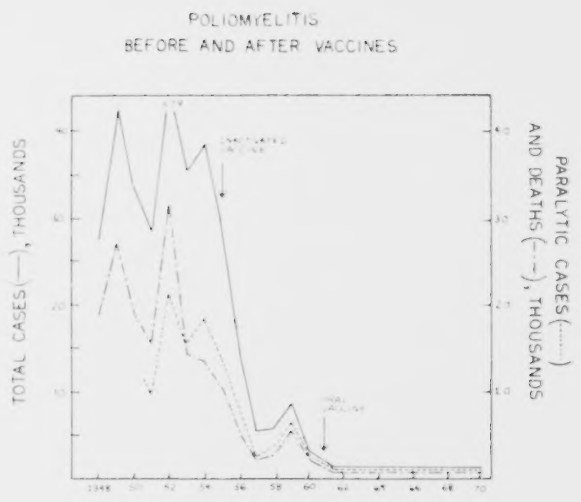


Figure 4-2. Total, paralytic and fatal cases of poliomyelitis in the United States during the 7-year periods preceding and following the introduction of the Salk vaccine. (From *The Economic Significance of the Prevention of Paralytic Poliomyelitis, 1955-1961.* Courtesy National Institutes of Health.)

Biological response modifiers (BRMs).

The activity of lymphocytes and macrophages can be enhanced or inhibited by a group of substances collectively called *biological response modifiers.* The nature of these substances varies from the products of certain microorganisms to products made by other lymphocytes and macrophages.

In the past decade, several substances have been described that influence lymphocyte differentiation and activity. These include thymic hormones—important in the differentiation of mature T lymphocytes from precursor cells; monokines and lymphokines—factors made and secreted by macrophages and lymphocytes, respectively; and the interferons—factors also made by macrophages and lymphocytes, but also by a variety of virally-infected host cells.

Thymic hormones. These hormones have been used to stimulate T-cell differentiation in patients who have an immunosuppressive malignancy such as Hodgkin's lymphoma, a cancer of the immune system. There are not enough data to assess the effect of this treatment on growth of cancerous cells.

Monokines and lymphokines. Activated macrophages synthesize and secrete monokines and antigen-activated lymphocytes synthesize and secrete lymphokines. These substances induce differentiation and increased activity in other lymphocytes.

Interferons. A great deal is known about the interferons. They were first discovered and characterized based on their common antiviral activity. They are made by virally-infected cells and "interfere" with further spread of the virus. They are also made by uninfected, activated macrophages and by antigen-stimulated lymphocytes.

Most interferons activate certain types of lymphocytes including B cells and natural killer (NK) cells. NK cells appear to be lymphocytes that are neither B nor T lymphocytes. They do not synthesize antibody. NK cells are very effective in killing a limited number of tumor cell types, notably tumors of the immune system. Their ability to kill can be increased two- to five-fold both in vitro and in vivo by interferon therapy.

Although all of the biological response modifiers discussed so far increase the activity of macrophages and lymphocytes, there are circumstances where the opposite effect is desired. For example, in transplantation of kidneys, heart, lung, or liver, the immune response to foreign histocompatibility antigens must be suppressed to prevent rejection. Many compounds can suppress the immune response, but they are nonselective and leave the individual at risk for infection and increased incidence of malignancy.

One of the new generation of immunosuppressive drugs that have some selectivity is cyclosporin A. This drug, recently licensed for use, has been very effective in prolonging the survival of organ grafts while not compromising to an unacceptable degree the overall immune responsiveness of the individual. Because the drug has some toxic side effects, the doses used do not permit permanent graft survival.

Summary

Exposure to an infectious organism (a complex antigen) may result in an adaptive response on the part of the host. Subsequent exposure to the same infectious organism will induce a more potent immune response. Establishment of active immunity or specific memory by natural exposure depends on many variables.

The physician may utilize specific vaccines to induce a state of immunity that is convenient, relatively safe, and predictable. The impact of active immunization by vaccination on human life in terms of social and economic factors is enormous. Although there are many vaccines in use, many more are highly desirable.

Biological response modifiers either enhance or suppress the activity of macrophages and lymphocytes. Applications of these reagents include immunotherapy of cancer patients, stimulation of lymphocyte maturation and activation in immunosuppressed patients, and the prevention of rapid rejection of organ grafts.

5. MALFUNCTIONS OF THE IMMUNE SYSTEM

Three major problems can occur in the immune system that lead to immune-related diseases, or immunopathologies. The first is *hypersensitivity*, in which the immune response to certain antigens may be abnormal. The result is damage to host tissues. These responses are characterized by allergies and hypersensitivities to drugs, poison ivy, and insect venoms.

The second, *autoimmune disorders*, results when immune responses are directed at the host's own tissues. These disorders may be either chronic and debilitating or acute and life-threatening.

Finally, the immune response to antigenic stimulus may be abnormally low. In some cases, the inadequate response is due to a primary defect in either the antibody response or the cell-mediated response. Sometimes both responses are inadequate. Furthermore, defects in the complement system or in the ability of macrophages and phagocytes to engulf and destroy pathogenic bacteria have been characterized in a number of patients. Those are collectively known as primary immunodeficiencies.

In addition to the primary immunodeficiencies, there are a number of diseases that affect other organ systems primarily, but that have a variable effect on the immune system. These secondary immunodeficiencies may be associated with drugs, overwhelming infection, infection with certain immunosuppressive pathogens and cancer—specifically, cancers of the immune system.

Allergies and hypersensitivities.

Ten to 30 percent of the population in the United States show an altered reactivity to certain antigens, that is, a hypersensitivity, or allergy. Epidemiologic studies show that these diseases cluster in families and that there is a genetic predisposition to allergic diseases. Allergic diseases, the most common form of immune disorder, include hay fever, asthma, hives, food allergies, contact hypersensitivities, drug sensitivities, and hypersensitivity to insect venoms.

Immediate hypersensitivity. One large category of these diseases is related to the production of IgE antibodies in response to environmental antigens. IgE, in contrast to most other classes of antibodies, is passively bound to the surface of circulating blood basophils and tissue-fixed mast cells. These cells express cell-surface receptors that have a very high affinity for IgE antibodies; very little IgE circulates in blood.

Both basophils and mast cells contain high concentrations of histamine packaged in cytoplasmic granules. The binding of antigen to specific IgE antibodies on the surface of these cells stimulates degranulation and release of this potent mediator of hypersensitivity. Histamine causes contraction of smooth muscle and dilation of neighboring blood vessels. Immediate hypersensitivity occurs in minutes and generally wanes in 30 minutes to one hour. The quick onset and severity of the reaction can be fatal, especially if it occurs throughout the body.

The reactions can be treated with a number of drugs that block the effects of histamine (antihistamines, not to be confused with antibodies). Hay fever, some types of asthma, hives, certain food allergies, and most hypersensitivities to insect venoms such as bee stings are due to this type of reaction, which is also known as anaphylaxis. Immediate treatment involves the use of drugs. However, desensitization therapy by vaccination with the appropriate antigen may be used to treat hay fever and bee sting sensitivity if the reactions are debilitating or life-threatening.

Hypersensitivity mediated by IgG and IgM. A second group of hypersensitivity diseases is caused by IgG and IgM antibodies. The onset of the reactions is measured in hours. In some cases, the reactions are induced by drugs that modify the host's own blood proteins or cells. For example, hypersensitivity to the classic drug used to treat malaria, quinine, is due to an antibody response to quinine-modified blood platelets. In this case the immune response leads to a transient drop in the concentration of platelets. The drop in blood platelets reverses when quinine is discontinued.

The inappropriate concentration of IgG (or IgM) antibodies, antigen, and serum complement components may also induce a type of hypersensitivity that appears in a few hours after exposure to antigen and persists until antigen is degraded (several hours to days). Farmer's lung is a disease caused by repeated exposure to thermophilic bacteria that reside in haystacks, composts, and silage at temperatures of 45° to 60° C. Circulating antibodies are formed against the bacteria. The antibodies combine with the bacterial antigens in the lung tissues and activate the serum complement sequence. Complement activation in the lung is so severe that mast cells degranulate and release histamine. In addition, complement activation results in further dilation of blood vessels and the accumulation of macrophages at these sites. The condition is treated by reducing exposure to the antigen, with corticosteroids, and occasionally with antihistamines.

Delayed hypersensitivity. Poison ivy and other contact hypersensitivities are caused by a T-cell-mediated response to host tissues that are modified by the contact agent. In the case of poison ivy or poison oak, the contact agent is an organic molecule of the catechol family. Other contact hypersensitivities may be due to heavy metals such as nickel or chromium in jewelry, or to the organic dyes used in hair dyes and food colorings.

T-cell-mediated responses to contact agents are slow to develop, typically taking 24-48 hours. That delayed reaction is due to the longer time required to move cells into the reaction site, as compared to the time required for antibody-mediated reactions. No antibody is involved in the delayed hypersensitivity reactions; the reactions are due to T-cell responses to specific antigen and the subsequent mobilization of macrophages to the reaction site. These reactions are seldom acute and generally resolve without any treatment.

The tuberculin test is an application of this type of hypersensitivity; a small amount of a purified antigen from *Mycobacterium tuberculosis* is injected into the skin. A

positive skin reaction (swelling and perhaps some redness) at 24-72 hours indicates T-cell immunity to tuberculosis. That may mean that active disease is present; it clearly indicates that the individual was exposed to *M. tuberculosis* in the past.

Autoimmune disorders.

Any immune response that results in damage to self may be considered an autoimmune disorder. There are instances of autoimmunities that do not result in damage to the host; those should not be considered autoimmune disorders. For example, the incidence of autoantibodies to a variety of tissues and tissue components gradually increases in both males and females with advancing age, yet most of these autoantibodies are of no clinical significance to the individual.

On the other hand, debilitating autoimmune disorders usually appear over a relatively short interval during the second to fifth decades of life. Moreover, these debilitating disorders occur more frequently in females than in males. Autoimmune disorders to a wide variety of tissue cells and cell components have been characterized.

All autoimmune disorders may be thought of as hypersensitivity reactions, where the host's own tissue is damaged as a result of the response. Autoimmune disorders may be grouped into three general types based on the kind of antigen that induces the response: (1) well-characterized environmental antigens that stimulate a tissue-damaging allergic response; (2) well-characterized self antigens against which an immune response is mounted; and (3) uncharacterized environmental or self antigens that stimulate a self-damaging immune response. The first type, hypersensitivities to well-characterized environmental antigens, was discussed in this chapter.

Autoimmune disorders that involve well-characterized self antigens. In some autoimmune disorders the target antigen is a well-characterized self cell or component. For example, there are two autoimmune disorders of the thyroid gland where the target antigen is well-known. In Hashimoto's disease, antibodies are formed against thyroglobulin, the major iodine-containing protein. In Graves' disease, antibodies are made to the thyroid cell-surface receptor for thyroid stimulating hormone. The antibodies inhibit hormone binding and, therefore, its biological activity.

Autoimmune disorders that involve unknown antigens. The third group of autoimmune disorders is caused by either environmental or self antigens about which nothing is known. Because the cause is unknown, these disorders are the most difficult to characterize and, most likely, will not lend themselves to any foreseeable treatment. Disorders of this type include rheumatoid arthritis and systemic lupus erythematosus (SLE).

Rheumatoid arthritis is a chronic, systemic, inflammatory disease that involves the synovial membranes of joints. The disease can be progressively disabling and disfiguring. Although many patients possess an IgM antibody that binds to their own IgGs (rheumatoid factor), IgG is not the primary stimulus of this autoimmune disorder.

WHAT CAUSES AUTOIMMUNITY?

The major unanswered question in autoimmune disorders is why an immune response is made to a self cell or cell component. There are at least three hypotheses. The first is that some tissues of the body are never learned as self by the immune system during development. The reason may be that those tissues are poorly supplied with lymphatics, as is the case with the lens of the eye, or that certain tissues are sequestered from the immune system, for example, tissue that forms sperm cells. If an injury or surgery such as vasectomy increases access of lymphocytes and macrophage to these tissues, these components may be viewed as foreign and an immune response will ensue. In the case of vasectomies, immune recognition and response to sperm cells occurs regularly. Fortunately, there is little or no adverse effect of antisperm antibodies on the individual.

A second hypothesis suggests that the immune response to a self antigen is due to a cross reactivity with an environmental antigen, that is, the environmental antigen and the self antigen are chemically similar. At least one autoimmune disorder, rheumatic heart disease, supports that hypothesis. This disorder represents a possible complication of infection with B-hemolytic streptococci (strep throat). The bacteria express an antigen similar to one expressed on human heart tissue. The immune response to this infection can sometimes, but not always, include antibodies that cross-react with and damage heart tissue.

The third hypothesis offered to explain autoimmune disorders suggests that the immune response to self antigens is normally tightly regulated. Breakdown in that regulation, according to the hypothesis, leads to autoimmune response.

Systemic lupus erythematosus is a generalized autoimmune disease; multiple organ systems and tissues may be involved. The disease is much more common among females than among males. It has been confused with arthritis many times, but laboratory tests can distinguish the two diseases. Its name derives from a characteristic rash that may develop in some patients over the bridge of the nose and around the eyes. This butterfly-shaped rash is reminiscent of a wolf's face, hence, lupus (wolf) and erythematosus (red).

This characteristic rash and other rashes are common in SLE patients, because their skin is unusually sensitive to sunlight in the ultraviolet spectrum. Laboratory studies show that these individuals frequently have autoantibodies to DNA, RNA, and a nuclear protein. Although these autoimmune antibodies are frequently associated with the disorder, they do not appear to induce the disorder. SLE is usually a chronic, progressively debilitating disease, but there have been occasional instances of acute, fatal cases.

Decreased immune response.

A number of conditions and factors have a negative influence on the host's immune system; they induce a decreased response to infectious disease and, perhaps, to cancer. These factors include inherent properties and biological activities of the infectious organism or cancer cells, age of the host, and the nutritional status of the host. These might be classified as having a secondary effect on the immune system.

Primary defects in the immune system, as illustrated in the opening example of this monograph, include the immunodeficiency diseases and cancer of immune-system cells such as the leukemias.

Properties of infectious organisms that influence the immune response. The relative immunogenicity of a pathogen depends first on the number and kinds of antigen expressed. Some antigens clearly induce a strong immune response. On the other hand, many infectious organisms have evolved mechanisms that protect them from the immune response and from elimination from the host. For example, some pathogens may shed their antigens or change their expression in response to an antibody or T-cell response. That reduces the efficiency of elimination.

In addition, the organism may change the antigen expressed. That, too, impedes immune recognition and elimination. This may occur over a period of years, as is the case for influenza A, where the virus undergoes complex antigenic changes that represent new genetic variants. On the other hand, it may occur within a relatively short time, as illustrated by the parasite *Trypanosoma brucei*, which causes African sleeping sickness. *T. brucei* changes its antigens sequentially during a single infection. The result of antigenic variation is incomplete elimination of the infectious organism from the host and host species and survival of the pathogenic species.

Sometimes the infection or malignancy causes generalized suppression of the host's immune system. If the infection or the tumor is overwhelming, the capacity of the immune system to process, respond to, and eliminate antigens related to the infection or tumor as well as unrelated antigens is severely reduced. The pathogen or tumor may also secrete substances that either suppress the immune response or inhibit the products of an immune response.

Certain viruses, notably measles, and HTLV-III (the virus associated with acquired immunodeficiency syndrome, or AIDS) cause a decreased response that is only partly understood. HTLV-III, for example, selectively infects and destroys the helper-T-cell population over a period of time and gradually decreases general immune responsiveness. Frequent infections and a high incidence of fatal Kaposi's sarcoma (a normally rare cancer) accompany those changes. The pattern of infections is similar to that seen for a deficiency in the cell-mediated immune system (see below).

Host-related factors that influence the immune response. The age of the individual is an important factor both in early life and advancing age. The fetus develops T and B lymphocytes by three to four months gestation and well-developed lymphoid organs by the fifth month. During that critical time in development, the fetus is protected by maternal IgG antibodies that can cross the placental barrier. Sometime during the second trimester the fetus is capable of making some IgM antibodies.

Maternal antibodies still in circulation at birth and IgA antibodies in milk provide protection for the newborn, but may also suppress the baby's own immune response to infection. That observation, and the fact that the newborn's ability to synthesize IgG rises slowly over the first year, may explain why the newborn is susceptible to certain bacterial infections during this time. At the other end of the age spectrum, gradual loss of thymic function is accompanied by a decrease in functional T cells and decreased ability to respond to certain infections.

Part of the answer to why some people get ill and others do not relates to the genetic constitution of the individual. The type and magnitude of an immune response to specific antigens depends on the inheritance of certain genes. Those immune response (or *Ir*) genes are often closely linked to the major histocompatibility complex (MHC) on chromosome six and are difficult to separate from class II genes (see chapter 3, "Initiation and Regulation of Normal Immune Responses"). Indeed, there are many disease associations with particular genes in this gene complex. The Ir genes have been distinguished from the genes that encode antibodies and antigen receptors on T cells. Ir gene products are thought to control immune recognition at the level of interactions between macrophages and T cells.

The nutritional status of the host also influences the immune response. Deficiencies in vitamins A and C have been shown to decrease the function of macrophages and T cells. Deficiencies in the minerals iron, zinc, and selenium have been reported to decrease immune function and elimination of infectious organisms. Malnourishment—in particular, protein deficiency—leads to a decrease in T cells in lymph nodes and spleen and to increased susceptibility to infection.

Finally, certain drugs such as steroids suppress the immune system nonspecifically. Although their effect may be mild and of little consequence for short-term treatment, prolonged use can cause increased frequency of infection. A similar situation occurs naturally during pregnancy. Researchers suspect that pregnancy-related proteins and hormones mildly suppress the host's immune response, which may explain the increased frequency of genito-urinary tract infections in pregnant women.

Immunodeficiency diseases.

These immune disorders are relatively rare. Their diagnosis is based on a past history of chronic or recurrent infections and infections that show incomplete response to treatment. Each type of immunodeficiency disease shows a characteristic pattern of infections.

B-cell deficiency. Immunodeficiency of the system that produces antibodies may be due to one of several defects in the production and maturation of B cells (and plasma cells) at any of several stages. The result is abnormally low concentrations of serum immunoglobulins, and infections with high-grade pathogenic bacteria from an early age.

Sometimes the defect is associated with an abnormally low concentration of B cells; other cases show that although there are normal levels of circulating B cells, the cells cannot synthesize antibodies efficiently. Many patients with B-cell deficiencies can be treated successfully with passive immunization (see chapter 4).

T-cell deficiency. Immunodeficiency of the cell-mediated system is also due to one of the several defects in the maturation and function of T cells. For example, abnormal development of the thymus and thymic tissue results in an abnormally low number of functional T cells. In contrast to patients with B-cell deficiencies, patients who have this disorder typically show a history of characteristic infections with low-grade pathogens such as viruses and fungi. There is very little specific treatment for T-cell deficiency.

Severe combined immunodeficiency (SCID). SCID represents abnormal functioning of both B cells and T cells and may be related to defects in the early differentiation of stem cells in the bone marrow. (These stem cells are the precursors to all lymphocytes.) Individuals who have SCID cannot live in a normal environment; they are susceptible even to microorganisms that are generally considered nonpathogens. They must be isolated in a sterile environment for life or until some satisfactory therapy is developed.

There has been some success in transplanting bone marrow (a source of normal stem cells) from family members who are matched for MHC type. Physicians must take great care to eliminate mature T cells from the donor bone marrow to prevent fatal graft vs. host disease, where mature T cells of the graft recognize and attack host cells as foreign.

There are also a number of characterized deficiencies in the systems that are used to eliminate antigen from the host. For example, defects in the ability of neutrophils to engulf and degrade pathogens have been observed in some individuals. In addition, a defect that leads to an abnormally low concentration of a particular complement component (protein) may also be associated with characteristic immunodeficiency.

Most of the deficiencies discussed thus far are characterized by an abnormally low concentration of a particular protein or cell. Very rarely is there complete absence of those components. In addition, these defects show a very strong pattern of inheritance. Those two observations suggest defects in genes and gene products that regulate the maturation and function of cells in the immune system or defects in the genes and gene products that regulate the level of a complement component, for example.

Acquired immunodeficiencies. The last group of immunodeficiency diseases is characterized by disorders that occur later in the life of an apparently normal individual. The one now attracting most attention is AIDS.

AIDS is induced by an environmental agent; the result is the loss of immune competence over time. HTLV-III, the virus implicated in AIDS, infects the helper-T-cell population. Sometimes these acquired disorders are temporary; others such as AIDS are progressive and often fatal diseases.

Cancers of the immune system.

Leukemias, related solid tumor lymphomas, and myelomas represent tumors of the immune system at different stages of lymphocyte differentiation. The leukemias are malignancies of either B cells, T cells, or monocytes (the immature blood-bone macrophages). The myelomas are malignancies of plasma cells, and, therefore, represent cancers of completely differentiated antibody-forming cells.

Increased incidence of infection is often a complication of these malignancies, but the exact relationship between the malignancy and suppression of the immune system is unknown. The physician is usually faced with the complicated problem of controlling both the malignancy and infection. The treatment is often immunosuppressive as well, which further complicates the clinical problems.

Summary

Allergic diseases are caused by unusually strong immune response to certain environmental antigens. The acute and most dangerous allergies are mediated by antibodies. Delayed hypersensitivities are mediated by immune T cells; although these reactions can be quite severe, they are generally not life-threatening.

The common IgE-mediated hypersensitivities show a strong pattern of inheritance in families in contrast to those mediated by other classes of antibodies and by T cells.

Autoimmune disorders are typified by reactions that result in damage to host tissue. Sometimes the antigen causing the disease is well-known, but often it is not. At present, treatment of patients with autoimmune diseases is targeted at relieving the symptoms, for example, reducing the inflammation of rheumatoid arthritis with anti-inflammatory drugs. For those disorders where the cause or self antigen is well-known, it may be possible to use a form of treatment directed at re-establishing immune regulation.

The immune system and its response can be adversely affected by:

(1) defects inherent in its maturation and function;
(2) factors related to the age, genetic composition, and general health of the host;
(3) extrinsic variables such as the effect of drug treatment and pregnancy; and
(4) factors related to the way in which pathogens evade immune elimination.

Some of those effects are either mild or can be treated easily, while others severely compromise the health of the individual and show little promise for therapy and control.

6. RECENT DISCOVERIES ABOUT THE IMMUNE SYSTEM

Progress in basic immunobiology has been quite rapid during the last two decades. Some of the more significant findings include the mechanisms by which antigen stimulates and influences the type of immune response, the processes by which cells of the immune system interact and communicate, the induction of immunologic memory in lymphocytes, and the generation of the enormous diversity in antigen-specific antibodies and T-cell receptors.

Antigens play an important role in the selection and stimulation of specific B and T lymphocytes. The biochemical structure of antigen influences how many and what kind of cells are selected. Recent findings suggest that specific substructures of a number of antigens may selectively stimulate B cells, helper T cells, or suppressor T cells. If those findings can be generalized to all antigens, it may be possible to modify an antigen that stimulates an IgE allergic response so that stimulation of suppressor T cells is favored rather than helper T cells. Thus, a special vaccine could be constructed to induce a suppressive immune response in individuals with life-threatening hypersensitivity to a particular antigen.

B cells, T cells, and macrophages collaborate to generate an immune response. How those cells communicate and interact has been elucidated in a series of discoveries. First, the sequence of events involving maturation and activation of these cells is now known in some detail, although information about early development at the level of the bone marrow stem cell is still lacking.

Second, researchers have identified a number of factors that influence maturation and activation of lymphocytes. Some of these have been characterized by structure and function, and a few have been isolated by recombinant DNA technology and gene cloning. When more of these cloned gene products are available, it should be possible to use them as biological response modifiers. For example, products of helper T cells could be used to influence the maturation of B cells that are blocked at a certain stage of development, as in certain immunodeficiency disorders. Products of suppressor T cells could be used to inhibit the response to self that is seen in certain autoimmune disorders such as myasthenia gravis and one type of diabetes.

Third, gene products of the MHC regulate the type of cell-cell interactions in the immune response (Figure 6-1). In responses that involve antigen, helper T cells collaborate primarily with cells that express class II, MHC gene products. In contrast, in an immune response to virally-infected host cells, cytotoxic T cells interact through viral antigens and class I MHC gene products expressed by the infectious host cells. Thus, two distinct subpopulations of T lymphocytes interact with other host cells preferentially based on the expression of antigen and either class I or II MHC gene products.

Fourth, the MHC class II genes are also closely associated with Ir genes. Ir genes control the level and type of immune response to a particular antigen. Most likely, that control is at the level of antigen-macrophage-T-cell interaction. Little is known about how the Ir genes influence these interactions. The importance of Ir genes to human health is illustrated by a number of known disease associations to particular alleles of class II (and some class I) genes.

Recent technologies related to the immune system.

Three technical developments have had enormous impact on research in immunobiology and biology in general. The first is the ability to hybridize a cell with a desirable immune function to another cell that can be grown in culture. These hybridized cells are called *hybridomas*. The second

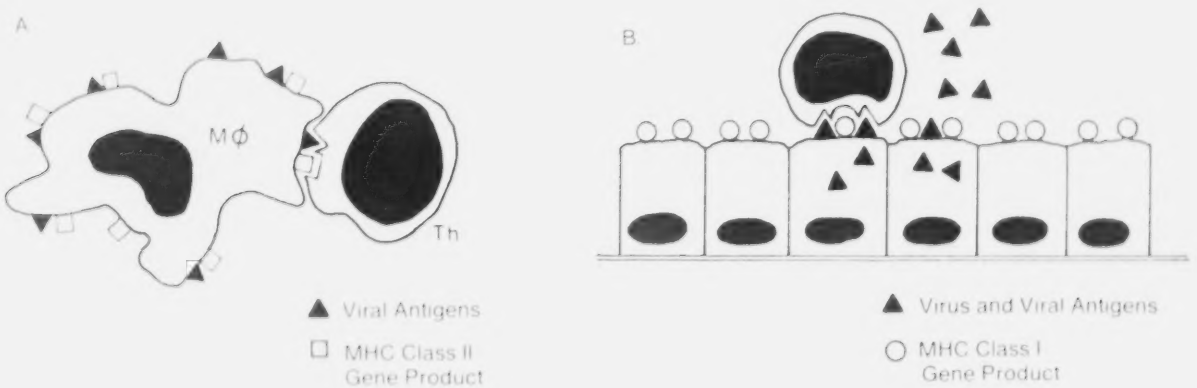


Figure 6-1. The role of class I and class II antigens of the major histocompatibility complex (MHC) in cell-cell communication. (A) A helper T cell (Th) binds to a macrophage (MΦ) that has engulfed a virus. The macrophage expresses viral antigens (▲) and MHC class II gene products (□) on its surface. This combination is required for recognition and binding by the helper T cell. (B) A cytotoxic T cell (Tc) binds to virally-infected epithelial cells by recognizing viral antigens and MHC class I gene products (○). (BSCS, 1986.)

DIVERSITY IN THE IMMUNE RESPONSE

One of the most exciting recent discoveries in immunobiology relates to the generation of diversity in antibodies and T-cell receptors. The genes encoding antibody molecules and T-cell receptors are limited in number and cannot account for the estimated 10^8 different specificities required to protect humans. How, then, is this number of antibodies generated from a limited number of genes? Molecular biology and recombinant DNA technology have provided some of the answers. Antibody diversity can be generated, in part, by a special sequence of recombinational events in the genes that encode these molecules. Beneficial somatic mutations superimposed on that process further increase diversity. Each individual inherits a limited number of genes for the construction of antibody molecules and T-cell receptors.

During the lifetime of that individual, multiple recombinations and somatic mutations operate on this limited number of genes in lymphocytes to generate necessary diversity of antigen-binding cells. Limited investigation has shown that these events do not occur in other somatic cells or in germ cells.

development is the ability to grow T cells and B cells in vitro with antigen and appropriate growth factors. The third is gene cloning by recombinant DNA technology.

The production of hybrid cells by cell-cell fusion has been possible for a number of years. However, in 1975, George Kohler and Cesar Milstein advanced that technology to include a method for fusing antibody-forming cells (B cells) to a myeloma tumor cell line. Normally, B cells do not grow in culture and soon die. The myeloma cell line grows indefinitely and may or may not secrete its own antibody. (The specificity of the myeloma cell antibody is usually not known.)

Production of hybridomas (Figure 6-2) involves immunization of a mouse with a specific antigen. The resulting immune B lymphocytes are then fused to the myeloma tumor cell line; the hybrids are selected under growth conditions where both the parent B cells and the myeloma cell line die. The surviving hybrids are screened for production of the antibody desired, and those cells are isolated by cell cloning. The end product is a hybridoma, a cell that has the antibody specificity of the parent B cell and the immortality of the parent tumor cell line.

Hybridomas may synthesize one or two antibodies, with at least one derived from the parent B cell, and possibly another from the parent myeloma cell line. Antibodies synthesized by an isolated clone of hybrid cells are referred to as *monoclonal antibodies.*

Monoclonal antibody technology has several advantages over production of antibodies by conventional immunization of animals. First, monoclonal antibodies are chemically uniform and do not vary from one production batch to

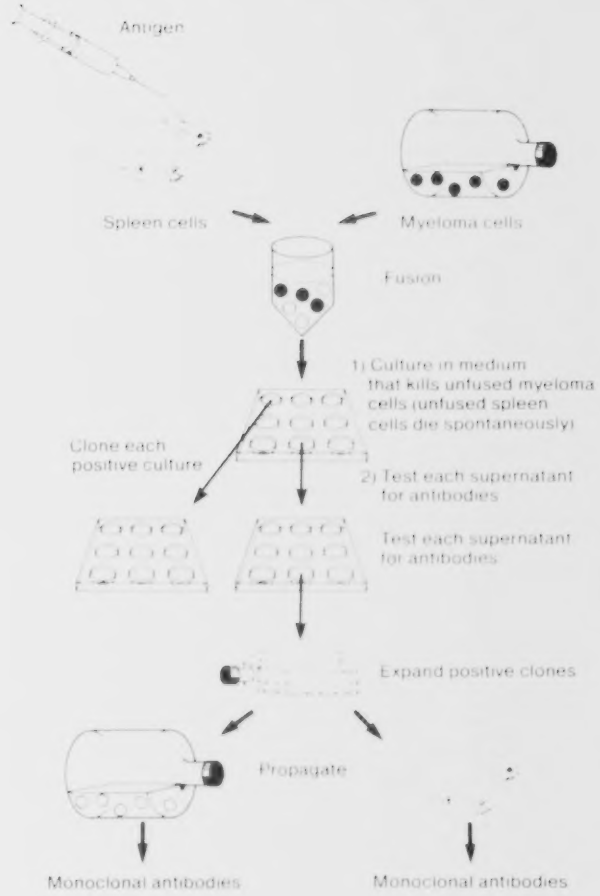


Figure 6-2. Procedure for producing monoclonal antibodies of a predetermined specificity. This technique was developed by Kohler and Milstein. (From John W. Kimball, *Introduction to Immunology*, Macmillan Publishing Company, Inc., 1983.)

another. Second, there is an unlimited supply of these antibodies, unlike those produced in individual animals. Third, the cloning technique used in their isolation allows the investigator to select monoclonal antibodies to relatively rare antigens expressed in a complex biological array. Monoclonal antibody technology is used in all branches of biology and medicine and has attracted much commercial interest.

For many years it was impossible to propagate B and T lymphocytes from peripheral blood in culture. Early attempts to grow them in vitro with media that could support the growth of other somatic cells in culture were uniformly unsuccessful. The discovery of factors that promote the growth and maturation of lymphocytes when antigen is also present made it possible to propagate these cells. It is now possible to isolate individual cells that have a specific function (helper T cells or cytotoxic T cells) by cloning methods.

Some of these cell lines will grow indefinitely in the presence of the suitable growth factors and occasional stimulation with antigen. Most, however, die out after a finite number of divisions. (Hybridoma technology is sometimes used to "immortalize" these cell lines.) The

importance of this technology is in defining the growth requirements of B and T cells.

Gene cloning by recombinant DNA technology has allowed molecular biologists and immunologists to isolate the genes that encode antibody molecules, the T-cell receptor for antigen, products of the major histocompatibility complex, and biological response modifiers such as the interferons and T-cell growth factor. This, in turn, has led to discoveries about the generation of diversity in antibodies and T-cell receptors, the structure and order of genes in the MHC, the structure and function of MHC gene products, and the large-scale production of interferons and T-cell growth factor for further study and clinical application. This approach is being used to isolate the genes encoding other factors related to lymphocyte growth and differentiation.

Future directions in immunobiological research.

The general goals of research in immunobiology have always been to increase basic understanding of the immune system and the immune response and to apply that knowledge to the treatment and prevention of disease.

Immunobiology is a dynamic field. There is still much to be learned about lymphocyte differentiation and development, cell-cell collaboration, immunologic memory, immune response genes, and somatic mutation as a mechanism for generation of diversity, to list only a few areas of intense investigation.

The interaction between the immune system and other organ systems. The immune system reacts to antigens and responds in the context of the whole human organism. It responds to and influences the function of other organ systems. For example, recent observations demonstrate that hormonal mediators synthesized by certain tissues of the body influence a variety of other tissues and organs, including cells of the immune system. Lymphocyte function may be enhanced or inhibited depending upon the type of hormonal mediator produced. In addition, hormones and pregnancy-associated proteins have been shown to regulate the immune response to varying degrees.

Preliminary data also suggest that the central nervous system can influence the responses made by the immune system. Psychologists and psychiatrists have long suspected that human behavior influences function of the immune system. There is now some experimental evidence in animals, including humans, to support that hypothesis. Clearly, this area of integrated biological study is in its infancy, but the striking parallels between the central nervous system and immune system have attracted recent attention and research.

Development of new vaccines. New technology makes it possible to approach the treatment and prevention of a number of diseases. For example, particular antigenic components from complex infectious organisms can now be identified and purified using monoclonal antibodies. Further, the genes encoding these components can be isolated by recombinant DNA technology. These two new technologies make possible a new generation of vaccines that can be prepared at greatly reduced cost, a fact particularly important to the health and economy of third-world countries.

One of several approaches being tested is the use of nonvirulent pox viruses as vectors for genes that encode antigens isolated from pathogenic organisms. The pox virus is one of the largest known viruses; its DNA is large enough that it can tolerate insertions of DNA encoding very large antigens. The recombinant pox virus can then be used as a vaccine to induce immunity to both the pox virus antigens and antigens encoded by the DNA inserted in the viral genome. It may be possible to insert 10 to 20 genes from different pathogens into one virus. This virus could then be used to immunize against all those pathogens by injecting the one vaccine. Thus, it might be possible before the end of this century to immunize against measles, polio, diptheria, whooping cough, tetanus, mumps, and rubella with one vaccine.

Transplantation of bone marrow. The treatment of some immune disorders may be possible with this new knowledge and technology. For example, a few patients with severe combined immunodeficiency can be reconstituted with bone marrow from a related individual. Because mature T cells in the donor graft can recognize and attack the host, it is necessary to remove mature T cells from the marrow to be transplanted. The effectiveness of this procedure can be monitored with monoclonal antibodies specific for mature T cells.

In a related application, the bone marrow from some leukemia patients has been treated outside of the body with monoclonal antibodies specific for the leukemic cells. Once the bone marrow has been removed for treatment, the patient is irradiated by Cobalt treatment to destroy remaining leukemic cells (and normal bone marrow cells). The treated bone marrow cells, ostensibly free of leukemic cells, are then reinfused to reconstitute bone marrow function in the patient.

The detection and treatment of cancer. Certain malignancies, notably well-differentiated B-cell leukemias and myelomas, may be susceptible to killing by lymphocytes that are not readily characterized as either B or T cells. Only patients with the malignancies listed above show a good clinical response to this treatment.

These laboratory findings and clinical trials are at a very early stage. If the observations are substantiated, however, this will be one situation where a biological response modifier—in this case, interferon—can be used to increase effector-cell function and to control the growth of a malignancy. The control of tumor growth and metastasis (spread) by immunotherapy has been a difficult problem. Perhaps new biological response modifiers will show some selective activity in controling the growth of yet another group of malignancies.

Finally, researchers have developed monoclonal antibodies that show some selectivity in detecting various types of cancers. Although those antibodies have not been proven to be absolutely specific for a particular malignancy, they have been useful in two applications.

First, they can be used to monitor changes in the concentration of tumor-associated antigens in blood, and, therefore, changes in the progression or regression of tumor growth in response to chemotherapy. Second, they can be

labeled with a radioactive isotope and detected by radiologic techniques after injection into patients. That technique has been used to locate tumors and tumor metastasis in patients.

Several researchers have proposed that cytotoxic drugs coupled to these antibodies be used to treat cancer patients by injection of the drug-antibody conjugate. However, monoclonal antibodies now available lack the absolute tumor specificity required for this treatment.

The use of immunologic techniques in other fields of biology.

Biologists outside the field of immunology have used antibodies in a variety of applications. These include the detection of specific proteins, enzymes, and carbohydrates in complex biological systems; detection of blood-group antigens in forensic analyses; and purification of specific biological macromolecules from complex mixtures.

Monoclonal antibody technology has found rapid and widespread application. This technology allows the biologist to select a single antibody-producing hybrid cell of desired specificity from a mixture of antibody-producing hybrids and clone that cell indefinitely. The power of the technique lies in the ability of the researcher to select an antibody-forming cell that synthesizes an antibody reactive with a single antigen in a complex biological array. Thus, a biologist interested in the developmental biology of sea urchins, for example, can produce a number of monoclonal antibodies that are specific for differentiation antigens expressed only at a particular stage in development.

Forensic laboratories and tissue-typing laboratories use new monoclonal antibody reagents to detect blood-group antigens and to type the major histocompatibility gene complex of donors and recipients for organ transplantation. These reagents may some day replace the antibody reagents now obtained from human volunteers. The immunogenetics laboratories that have developed many of these new monoclonal antibody reagents have also detected new genetic variants in humans. Some of those may relate to the immune response genes discussed earlier.

Further, with this battery of reagents that detects increased variability in the MHC, it is now possible to refine paternity testing. Until recently, typing of ABO blood groups was the only legally acceptable material used in paternity cases. Those data could be used to exclude the putative father, but could not be used to prove paternity. Typing for MCH gene products (HLA typing) is now standard laboratory procedure, and the results are now accepted as evidence in paternity cases. HLA typing is also used only to exclude a putative father and cannot prove it conclusively. When the battery of antigens detected by an ever-increasing number of antibody reagents is large enough, however, it may be possible to prove paternity.

Reproductive biologists have attempted to devise new ways to control fertility, including the potential use of antifertility vaccines. Candidate antigens for such vaccines include proteins unique to the zona pellucida of the unfertilized ovum and an alternative form of a common enzyme unique to sperm. The quantity of these proteins and enzymes for use in vaccine production is severely limited, however. Monoclonal antibodies have been made to these proteins for use in identification and purification. In addition, these monoclonal antibodies can be used to identify indirectly the genes that encode these proteins. This has led to the cloning of at least one of the genes for the antigens that surround ova. If these findings are confirmed and extended, large quantities of these antigens may soon be available for testing as possible vaccines. An effective vaccine would be one that induces an immune response to the unfertilized ovum and prevents fertilization by sperm.

Summary

New information and technologies developed in immunobiology and molecular biology have led to many insights into the way the body responds to infectious organisms, to cancer, and to organ and tissue transplants. Ongoing research has provided preliminary answers to enduring questions such as those concerning the generation of antibody diversity. New, basic knowledge has found rapid application in problems relating to human health and disease. The application of recombinant DNA techniques may result in the development of a new type of vaccine that permits immunization against multiple pathogens at one time.

GLOSSARY

Acquired immune deficiency syndrome (AIDS). An acquired immune deficiency disease resulting in loss of helper-T-cell function. Thought to be induced in part by a retrovirus. Results in gradual loss of immune competence and increased incidence of infections and particular malignancies.

Acquired immunodeficiencies. See immunodeficiency disease.

Active immunization. Stimulation of an individual's own immune system by introduction of an antigen into the body.

Allergies. Hypersensitive states acquired through exposure to specific environmental antigens (allergens).

Antibiotics. Substances produced by a living organism—for example, the penicillin molds—that are toxic to bacteria. They are not toxic to viruses.

Antibodies. Glycoproteins, produced by lymphocytes, that can bind specifically to antigen.

Antigen. Any substance that stimulates a specific immune response.

Antihistamine. One of several types of drugs which can be used to inhibit further release of histamines.

Autoimmune disorders. Clinical disorders resulting from immune responses against self antigens.

B cell. A B lymphocyte that can be stimulated to produce antibody.

B-cell deficiency. A condition in which antibody-mediated immunity is impaired.

Biological response modifiers. Drugs, simple polypeptide hormones, or complex biological molecules and structures that stimulate the immune system in a powerful but nonspecific way.

Cell-mediated (cellular) immunity. Immune responses that involve T cells and do not require antibody.

Complement. A group of serum proteins that, when activated by antibodies bound to antigen, can destroy the antigen.

Cytotoxic T cells. T lymphocytes that have been specifically sensitized and are capable of killing target cells expressing specific antigens.

Delayed hypersensitivity. See hypersensitivity.

Effector. Cell or protein molecule that carries out the functions of the immune system.

Fab region. The variable portion of an antibody molecule that binds antigen.

Fc region. The constant portion of an antibody molecule that binds to specific receptors on effector cells or complement proteins.

Histocompatibility antigens. Cell-surface molecules characteristic of an individual that stimulate rejection of tissue transplants.

Humoral immunity. Immune response that involves antibody.

Hybridomas. Cells produced by fusion of normal B lymphocytes with a myeloma tumor cell line to "immortalize" the antibody-producing capabilities of the parent.

Hypersensitivity. A state of immunity that results in a tissue-damaging immune response upon exposure to a specific antigen. The response may be immediate, as in response to a bee sting, or delayed, as in response to poison ivy.

Idiotype. The characteristic structure of the antigen-binding region of an antibody molecule that differentiates it from all other antigen-binding regions. This is the part of the antibody molecule that attaches to the antigen.

Immediate hypersensitivity. See hypersensitivity.

Immunodeficiency disease. A deficiency in immune response, either in that mediated by antibody, immune T cells, or both. May be inherited or acquired, as in acquired immune deficiency syndrome (AIDS).

Interferons. Biologic response modifiers (q.v.) that are effective in combatting viral infections.

Leukemias. Neoplasms (tumors) of the immune system, for example, T-cell leukemias and B-cell leukemias.

Lymphocyte. A small, spherical cell from 7-12 um in diameter with a large nucleus and little cytoplasm. B lymphocytes may mature into antibody-forming cells. T lymphocytes may differentiate into helper T cells, cytotoxic T cells, or suppressor T cells.

Lymphokines. Polypeptides released by T cells that have come into contact with specific antigens. Lymphokines increase the activity of certain lymphocytes.

Macrophages. Phagocytic cells distributed widely in the vertebrate body. They are important in the processing and presentation of antigens to lymphocytes and in the ultimate elimination of antigen from the host tissues.

Memory. The capacity of the immune system to respond much faster and more powerfully to subsequent exposures to an antigen than it did at first exposure.

Monoclonal antibodies. Antibodies produced by and isolated from a single antibody-producing cell and its progeny (clone).

Monokines. Polypeptides secreted by activated macrophages (q.v.). Monokines increase the activity of certain lymphocytes.

Neutrophils. Phagocytic white blood cells that are especially important in combatting acute bacterial infections. They are an important component of nonspecific immunity (q.v.).

Nonspecific immunity. Immunity such as that provided by the skin, which provides a general barrier to infection.

Passive immunity. Transfer of immune serum (or antibodies) or cells from one individual into another.

Phagocytes. White blood cells (mainly macrophages and neutrophils) that ingest foreign objects.

Rh disease (hemolytic disease of the newborn). An incompatibility of Rhesus (Rh) antigens between a mother and her fetus that may result in the production of maternal antibodies that bind to and cause the destruction of fetal red blood cells.

RHOGAM. A commercial preparation of anti Rh+ antibody given to an Rh− mother delivering an Rh+ child. Passive immunotherapy of this type prevents sensitization of the mother to Rh+ red blood cells and reduces the risk to future Rh+ fetuses.

Secondary response. The immune response generated on second (and subsequent) encounters with an antigen; it is faster and greater than a primary response.

Severe combined immunodeficiency. A congenital immunologic deficiency in which both T lymphocyte and B lymphocyte development and function are deficient.

T cell. A lymphocyte which matures in the thymus.

T-cell deficiency. A condition in which cell-mediated immunity is impaired.

Thymic hormone. Polypeptides produced by the thymus that are involved in the maturation of T cells.

Toxin. A poisonous substance produced by certain microorganisms such as the tetanus bacterium.

Toxoid. A toxin (q.v.) that has been altered chemically or physically to destroy its toxicity and maintain its immunogenecity for use as a vaccine.

IMMUNOLOGIC AND EDUCATIONAL CONCEPTS ADDRESSED IN STUDENT ACTIVITIES

ACTIVITIES	CONCEPTS: diversity	memory	self v. nonself	adaptive response	protection	regulation	inappropriate immune response	science as inquiry	science, technology, society issues
A. Why Do Some People Get Sick?	P	P	-	E	P	-	-	E	P
B. Identification of Blood Components	E	-	E	P	-	-	P	E	E
C. What Provides Immunity?	-	P	P	E	E	P	-	E	-
D. The Mystery of the Alpine Slide	P	P	-	P	-	-	E	E	P
E. Acquired Immune Deficiency Syndrome (AIDS)	P	-	-	P	-	P	-	P	E
F. The Cheetah—A Potentially Extinct Species?	P	-	E	E	-	P	E	E	P

P=concept present
E=concept emphasized

ACTIVITY A. WHY DO SOME PEOPLE GET SICK?

Focus

This activity involves students in a strategy that will lead them to develop their own definition of immunity.

Objectives

Students will have opportunities to:

1. define and give several examples of immunity;
2. propose hypotheses to explain observed data; and
3. analyze the history of a disease (plague).

Materials and advanced preparation

Activity A consists of six readings (parts A-F), which must be presented sequentially. Those readings are located in the student pages found in section III of this monograph. Since it is important that your students consider only one reading at a time, be certain to share only the relevant information. This may be done by reproducing the pages and handing out only the appropriate part. A preferable option is to project each student reading on an overhead for discussion. The chalkboard is a less-attractive option. We strongly suggest something other than a strictly verbal presentation of the student narrative.

Relevant portions of section I

Chapter 1: Recovery from infection leads to long-lasting immunity. (page 2)
Chapter 2: The immune response is specific. (page 3)
The immune response has memory. (page 3)

From the field test:
Alternative suggestions for conducting the activity

☐ Provide introductory comments about the immune system and the immune response, perhaps in the broad context of a discussion about infection; introduce briefly some of the examples of the functions of the immune system that are given in section 1, chapter 1.

☐ Increase student participation by having students do all parts of the activity in small groups (2 to 3 students); each group then reports its findings which are listed on the chalkboard for analysis.

Suggested scheduling

Average preparation time for teaching this activity = 50 minutes; average time for teaching this activity the first time = 50 minutes.

Directions for conducting the activity

The format for this activity follows the procedure developed by Joseph J. Schwab, University of Chicago, and presented in his book *The Teaching of Science as Inquiry,* Harvard Press, Cambridge, MA, 1962.

The activity as presented to the student is incomplete. There are gaps in information that the student is asked to fill. That may require that the student draw a conclusion from the data presented or develop a hypothesis to account for the data. A good strategy is to allow students to discuss the various questions in small groups and then ask each group to present its ideas to the entire class.

The teacher should not supply information to fill the blanks. The objectives of the activity go beyond the learning of content. Students can discover through the kinds of problems posed, and through their ability to contribute to the solution of those problems, that science is more than merely learning from others what others know. They also learn that through participating in such activities, the quality of the activity itself may be shaped and improved. Students may develop skill in the interpretation of data and the understanding of scientific knowledge.

A more complete discussion of the background and rationale of this kind of learning strategy is presented in pages 305 to 310 in the BSCS *Biology Teacher's Handbook,* 3rd edition, Macmillan, New York, 1978.

Part A

Students should develop the notion that in most severe epidemics large numbers of people, frequently the majority, survive. If 25 million died of the plague in fourteenth-century Europe, then 75 million survived. Some reasons for this might include the following (list them on the chalkboard as they are given):

- They did not come in contact with the plague, that is, they did not encounter infested rats.
- They did not come in contact with the disease carrier—the fleas.
- They were naturally immune to the disease. (This raises the important concept of differential genetic susceptibility to infection.)

Students will likely provide more reasons. Accept all of them, even if they are not possible. If necessary, the incorrect responses can be eliminated later in the activity, with discussion about why they are incorrect. The notion of genetic variation is particularly important and recurs in part D.

Part B

Some reasons for this pattern might be:

- Most people lived along trade routes.
- Rat populations were large along trade routes.
- Rats, the carriers of the infected fleas, were transported by ships to most areas along the trade routes. Ask students to recall major historical events from this period that might have contributed to the spread of the disease. It is likely, for example, that rats were transported by ships returning from the Crusades.

Part C

Issues that might arise in the discussion include:

1. Effective quarantine measures: plague can be prevented by shielding humans from infected, flea-carrying rats. You might give the following information to your students: pneumonic plague, which is caused by the same bacteria that cause bubonic plague, is transmitted directly from one person to another in sputum. With that information students should respond that shielding humans from individuals with this disease will prevent its spread.

2. Gradual improvement in housing: this was another measure that kept humans from coming in contact with rats and their infected fleas.

3. A rapid decline in the black-rat population caused by fierce competition from the hardier brown rat carried the infecting flea just as did the black rat. The "sewer rat" connotation would indicate that the chances of human contact would be less with the brown rat than it was with the black rat, which was more of a "house rat."

Part D

Issues that might arise in the discussion include:

Natural selection; if you have dealt with the concept of natural selection, no additional information to the students should be necessary. If not, a brief explanation of the process will be necessary. Students should develop the idea that if the people who survived the plague did so because of some internal protection (immunity), that protection might have been passed on to their children, their children's children, and so on.

The persistence of plague involves some interesting interactions between the infectious agent, vectors, and the growth of human populations. Share the following information with your students:

Plague is caused by the bacterium *Yersinia pestis*. The bacteria are spread by fleas that feed on infected animals such as rats. The outbreaks of plague in the Rocky Mountain West have largely been associated with the common rock squirrel, *Spermophilas variegatus*, which harbors the flea *Diamanus montanus*.

As housing developments encroach on the squirrels' habitat, the opportunities for exposure to the disease increase. The death of the 14-month-old girl in Colorado was traced to rock squirrels under her house. Ask students to hypothesize how human habitation increases the amount of contact with squirrels. List the students' hypotheses on the board. Two of the most obvious hypotheses are:

1. houses and other human structures, and food (garbage), attract the squirrels, and
2. human habitation drives off natural predators (foxes, coyotes, rattlesnakes, hawks, owls) that would normally control the growth of the squirrel population.

Ask students how local health authorities might control the spread of plague. Some possibilities include:

- dusting squirrel habitats with poisons that kill fleas
- public education that encourages people to avoid squirrels, especially May through September, when the squirrels and fleas are most numerous

Additional information about plague:

- Prairie dog communities in the West also carry fleas that harbor *Y. pestis*. Many new housing developments are built near these communities, which increases contact with the vectors.
- Fleas can survive about two weeks without a host, for example, after a prairie dog community is destroyed by plague. They then seek other hosts, such as dogs or humans if they are in close contact.
- The eastward spread of the disease appears to follow waterways such as the South Platte River in Colorado. This is presumably due to the preference of the rock squirrel for habitats near the waterways.
- The early symptoms of plague are chills, headache, and high fever (102°-104°). Plague responds well to treatment with antibiotics, if treatment is provided in time. Many physicians are unfamiliar with plague, but educational programs along the front range of the Rockies are improving this situation. The 14-month-old girl was misdiagnosed and so was not treated properly.

Part E

Students may share some of the following information about chicken pox:

- If you develop the disease, it is usually soon after you have been in contact with someone who had the disease or soon after your contact came down with the disease.
- You only get the disease once.
- Older people who get the disease can be very sick while they have it.
- It is best to have it when you are young; in fact, some parents deliberately expose their children to the disease in the hope that it will develop while they are young, when the chance of any real harm is very slight.
- Having chicken pox will not prevent one from getting the measles or mumps.

Part F

The product here is a list of questions that will lead students to other activities. Do not ask for answers at this point. The emphasis should be on generating as many questions as possible. A few that students should raise include:

- Why do some people get sick while others do not?
- Why do we get immunized against some diseases and not others?
- Do other organisms have immune systems?
- Can you be born with a disease?
- Why do some people get sicker than others with the same disease?
- Why do antibiotics work against some disease and not others?
- Why do some immunizations confer life-long immunity, while others require "boosters"?

Suggested test items

During the Great Plague of London, people did a variety of things to protect themselves from the plague. Some were effective, some were not. Evaluate these behaviors according to the following key.

KEY: A. Would likely *decrease* the chance of getting plague.
B. Would likely *increase* the chance of getting plague.
C. Would likely *not be effective* one way or the other.

1. (C) Many people refused to drink water from the wells of London.

2. (B) Some people gathered together in large groups protesting that the authorities were not doing enough to protect them.

3. (A) Many people left London and moved to very isolated areas.

4. (B) Thousands from rural areas went to London.

5. (B) Some locked themselves in cellars away from the light.

6. (C) Many consulted with witch doctors, astrologers, and fortune tellers.

To protect a human population from the plague, all but one of the following would be effective. Which one would *not* be:

A. Isolate people from one another as much as possible.

B. Reduce the rat population as much as possible.

*C. Boil all drinking water.

D. Maintain the health of the population through good nutrition habits.

"Individuals who have a natural immunity to a particular disease will survive an epidemic of this disease and will pass the immune characteristic along to their offspring by a process of natural selection." This is a statement of

A. data

*B. theory

C. fact

D. experiment

A simple definition of immunity is "once you have chicken pox you will never get it again." That is not true for the common cold. You know you can get a cold two or three times a year, every year. Which of the following could best explain why this is true?

A. The cold virus does not stimulate the immune system to operate.

B. The cold virus destroys the immune system.

C. Colds are caused by a variety of environmental conditions like cold drafts, wet feet, chills after exercise, etc.

*D. The common cold is caused by a large variety of viruses.

ACTIVITY B. IDENTIFICATION OF BLOOD COMPONENTS

Focus

In this activity, students investigate blood components that may interact under specific conditions. The primary concerns are immune substances of plasma and their reaction with specific antigens on cells.

Objectives

Students will have opportunities to:

1. discover that one component of blood serum will react specifically with another component—red blood cells;
2. compare variations in reactivity;
3. devise answers to questions about specificity as it applies to blood transfusions;
4. understand antibody/antigen binding and agglutination; and
5. learn about tissue transplantation and associated personal and societal problems involved with that type of surgery.

Materials and advanced preparation

You will need the following materials:

microscope slides (clean)
paper towels
human anti-A and anti-B antiserum
blood-letting lances (sterile)
alcohol prep pads
toothpicks
*whole human blood (types A, B, AB, and O) for students who do not wish to use their own blood

Relevant portions of section I

Chapter 2: The immune response is specific. (page 3)
Antibodies are produced in response to antigen. (page 3)
The structure of an antibody leads to its dual function. (page 3)
The Immune System Contains Both Fixed and Circulating Cells (box, page 7)
Chapter 3: Histocompatibility Antigens Induce Graft Rejection (box, page 12)

From the field test:
Alternative suggestions for conducting the activity

☐ Follow the discussion of students' conclusions with a general discussion of blood typing, including problems associated with Rh incompatibility.

☐ Assign "A Life on Standby" as an individual reading, perhaps as homework.

☐ Assign the following reading: *Blood: The River of Life*, by Donald R. Avoy, MD, American Red Cross, 1976.

Suggested scheduling

Average preparation time for teaching this activity=60 minutes; average time for teaching this activity the first time=85 minutes.

Directions for conducting the activity

This is not a traditional blood-typing exercise. Instead, students observe and suggest ideas about what they see: clumping or agglutination of red blood cells. Prior to the activity, mask the labels on the antiserum vials and relabel antiserum A as substance 1, and antiserum B as substance 2.

Also mask the labels on the vials of human whole blood as component a for type A, b for type B, c for type AB, and d for type O. Keep a key to help you and the students remember what these numbers (1 and 2) and letters (a, b, c, d) correspond to.

Once the students have performed the "typing," record their data on the board and compare with their neighbors their clumping (or lack of clumping) with a particular substance.

Divide the class into groups of three students each and have them suggest possible responses to the questions under the heading "Results and Interpretations." Allow about 15 minutes (adjust time accordingly), and then have one member of each group share that group's ideas with the class.

Responses to questions under "Results and Interpretations"

a. Clumping or agglutination should be obvious except for type 0 individuals. Students should observe some variations.
b. Responses will vary; the objective is to have students relate what they see to antigen/antibody interaction.
c. Clumping of red blood cells in circulatory pathways may cause death.
d. Antibody/antigen specificity.

Antibodies are carried in the liquid portion of the blood. The antigens that concern us in this activity are on the surface of the cells. The clumping (agglutination) is caused by the cross-linking of antibodies with the red cells that have the corresponding antigen. For example, anti-A antibody cross-links with red blood cells that have A antigens on their surface. Anti-A antibody will not cross-link with cells that

express only B antigens. The agglutination reaction is the classic test for blood type.

Be certain to distinguish between clumping (agglutination) and clotting. Clumping involves the binding of an antigen with a specific antibody. There is no such involvement of antigen and antibody in the clotting process.

You might wish to tell students that they have rediscovered what Karl Landsteiner first discovered in the early 1900s. He was awarded the Nobel prize in 1930 for his work over several decades on blood groups.

A Life on Standby

Have students read the section titled "A Life on Standby." Divide the class into groups of three to four students and have them consider the items under "Questions for Discussion." Twenty minutes (adjust time accordingly) should be adequate. Have one member of each group share that group's thoughts with the class. Help students relate similarities between blood matching for transfusion with tissue typing for transplants.

Responses to questions under "A Life on Standby"

1. It is difficult to find a liver that will not be recognized as foreign by the recipient of a transplant. First, then, a donor must be found, then proper tissue matching must occur prior to transplant surgery. This is HLA typing and is similar to blood typing.
2. There are several major concerns such as the surgical risk to the patient from anesthesia, infection, and another major concern of rejection.
3. Immunosuppression generally decreases the chance of rejection of the grafted tissue. However, infection is always a concern.
4. As stated above, an undesirable side effect of immunosuppression can result in dangerous infections as the immune system is immobilized.
5. This is an opinion item; responses will vary. The teacher's opinion should be avoided here.
6. Ideas will vary; accept all responses.
7. This is a classic problem in the allocation of scarce medical resources. There are no "correct" answers.

   Help students with question c. This question will help clarify some of the characteristics that society uses to place values on human life and to determine the quality of life.

   This dilemma also highlights the problem of assigning responsibility for such decisions. Who should decide? One of the purposes of public education is to enable citizens to participate effectively in the establishment of policies that help manage such difficult issues.

Extensions

After you have dealt with the questions, clarify any confusion and share with your students information about antigens, antibodies, agglutination, and transfusion compatibility of the ABO blood groups.

Once the activity has been concluded, you may want to share the following information with your students about transplantation and tissue typing, HLA antigens, and immunosuppression and cyclosporin A.

Transplantation/Tissue Typing

Researchers have acquired the ability to remove a human heart, liver, kidney, and other selected tissue from the body of a donor and transplant it into another person. Gradually, the transplanted organ will grow stronger in the performance of its function, but only for a time.

Soon after the transplant has been completed, small fragments of the grafted tissue escape into the bloodstream. Some of those fragments make their way to nearby lymph nodes where the recipient's T cells recognize that the grafted tissue is not "self." Similarly, T cells in the blood come into contact with the graft itself. Those T cells initiate an immune response, releasing interleukin-2, and gamma interferon, stimulating phagocytes and killer cells, all of which attack their target: the newly-transplanted tissue. Unless that immune response is stopped, the recipient's defense system will destroy the very tissue or organ required for survival. Within several weeks, the rejection process will be complete.

Early transplants of kidneys were successful primarily between identical twins. Because identical twins express identical antigens, the recipient's immune system would recognize the new tissue as self and thus accept the graft. The rejection of transplants has made the treatment of some diseases a challenging problem for physicians.

There is nothing surprising about rejection; the immune system is performing its fundamental role, that is, the elimination of foreign matter that invades the body. The immune response to a transplant is no different from the attack against a bacterial or viral invader. Although rejection of the first skin graft may take 10 to 14 days, a second graft from the same donor will be rejected in only two to four days. Memory T cells, already present from the body's first response to a skin graft, will rapidly reject the second graft, as they would any invader that they have encountered before.

HLA Antigens

The major antigenic stimulus for rejection involves several related antigens on cell surfaces. These are known as histocompatibility antigens. Those antigens were discovered originally in mice and were discovered first in humans in the late 1950s. Because they are on white blood cells, they have come to be known as human leucocyte antigen, or HLA. Their structure in humans is determined by genes at the major histocompatibility complex, on chromosome 6. HLA antigens play a major role in determining acceptance or rejection of all types of human transplants. Transplants between identical twins are almost always accepted, because those individuals share identical HLA antigens.

Transplants between nonidentical individuals, however, even between parents and their offspring, are usually rejected. This rejection is due to differences in HLA antigen patterns.

Immunosuppression

The conventional weapons used to prevent rejection of transplants have been drugs and radiation treatment that suppress the immune system by interfering with the division of cells of the immune system. By blocking the development of such cells, the patient is left without the ability to fight any invaders. In addition, the treatments often produce undesirable side effects. If the transplanted tissue is to survive, physicians must severely suppress the patient's immune response, but this immunosuppression exposes the patient to dangerous risks of developing potentially fatal infections.

One way to avoid immunosuppression is to select donors and recipients whose histocompatibility antigens are similar. In the past, physicians have sought donors among family members. Among siblings (brothers and sisters), the chance of finding similar histocompatibility antigens is about one in four. When genetically similar family members are not available, transplant patients must depend upon unrelated individuals, and the chance of finding a good match is less than one in one thousand. Today, immunologists have begun to find ways to measure the histocompatible similarities between unrelated persons, thus increasing the chances of finding the proper match for transplants.

Cyclosporin A

Transplant surgery has advanced greatly in the last several years with the unexpected discovery of a revolutionary new drug. This drug, cyclosporin A, blocks the growth and function of cells of the immune system. Unlike other immunosuppressive drugs, however, cyclosporin A does not appear to kill lymphocytes. By blocking an important link in the immune cycle, cyclosporin A seems to disrupt certain important immune responses. Cyclosporin A thus seems to block the function of immune cells, while leaving other cells of the body undisturbed. That eliminates many of the toxic side effects produced by other immunosuppressive drugs, which often left patients seriously disabled. These drugs affected all dividing cells, causing anemia.

Cyclosporin A has dramatically reduced the risk of rejection in transplant surgery. However, it still blocks a full range of normal immune responses, and patients on the drug still run the risk of severe infection. The ideal transplant treatment would involve only those cells of the immune system that are directed against histocompatibility antigens of the graft itself, leaving other cells of the immune system free to protect against infection. Unfortunately, the ideal immunosuppressive drug has not yet been found.

References

Introduction to Immunology, John W. Kimball, Macmillan Publishing Company, New York, 1983.
In Self Defense, Steven B. Mizel and Peter Jaret, Harcourt Brace Jovanovich, New York, 1985.

Suggested test items

Bob was feeling awful, with a headache, a fever, and a sore throat. His father was worried, so he took him to the doctor. The doctor did a lot of tests on Bob, which required drawing a sample of blood from his arm. Some of this blood was sent to the laboratory for testing. Some of it was separated into cells and plasma; the nurse froze the plasma in the freezer at the doctor's office. The doctor gave Bob a shot of penicillin, a prescription for some penicillin pills, and sent him home to bed. Five days later Bob was well.

However, because the doctor wanted to see Bob again, his father took him back to the doctor the next week. This time, she took another blood sample from Bob, and sent the plasma from that sample, as well as the sample from the first visit, to the lab for testing.

The lab technician mixed samples of Bob's plasma with three different kinds of bacteria. He then looked to see if Bob's plasma would clump any of the bacteria. He also took plasma from a person that had not been sick (normal plasma) and tested it on the same bacteria. The lab reported the following results:

Plasma sample	Bacteria A	Bacteria B	Bacteria C
Bob's first	nothing	clumped	nothing
Bob's second	nothing	clumped	clumped
normal	nothing	nothing	nothing

Questions

1. How do you explain the results with bacteria A?
2. How do you explain the results with bacteria B?
3. How do you explain the results with bacteria C?
4. Which bacteria was responsible for Bob's disease?
5. Why did the lab also test the plasma from a person who had not been ill?

Some answers

1. Bob has never encountered bacteria A and has never made antibodies against it.
2. Bob had encountered bacteria B and has antibodies in his plasma that will clump those bacteria. However, bacteria B did not cause Bob's illness because he had antibodies to them on the day he got sick. If his disease was due to bacteria B, then the antibodies would have prevented him from getting sick.
3. On the first visit, Bob did not have antibodies against bacteria C, but on the second visit he did. Thus, during the time between the visits, he developed an immune response to bacteria C, which means that he was infected with bacteria C. Thus, bacteria C probably caused his disease.
4. Bacteria C (see previous answers).

5. The normal plasma serves as a negative control so that the lab will know if the bacteria will normally clump without the presence of antibody. (Note: There should also be a positive control, that is, an antibody that will clump each of the three kinds of bacteria. An alternative explanation to the results with bacteria A is that these bacteria never clump, no matter what you do to them.)

ACTIVITY C. WHAT PROVIDES IMMUNITY?

Focus

This activity acquaints students with the concept that the human immune system has at least two components—humoral and cellular—that are closely interrelated. The intent of this activity is to help students interpret data and come to their own conclusions. It is important that the teacher not present information until that information is necessary for interpretation of the data.

Objectives

Students will have opportunities to:

1. interpret evidence related to the transferability of immunity; and
2. see that there is a relationship between the known components of the human immune system.

Materials and advanced preparation

Make enough copies of the worksheets to have one for each group. The worksheets are included in the student pages found in section III of this monograph. In addition, use the black-line masters included on pages 37-38 to make overheads of Figure C-2 and Figure 3-2.

Relevant portions of section I

Chapter 1: The immune system helps us recover from disease. (page 2)
Recovery from infection leads to long-lasting immunity. (page 2)
Chapter 2: Antibodies are produced in response to antigen. (page 3)
Antibodies work with cells or serum proteins (complement) to destroy antigens. (page 5)
Chapter 3: What happens the first time: a primary response. (page 9)
T cells distinguish self from nonself. (page 11)

From the field test: Alternative suggestions for conducting the activity

☐ Review the development of classic germ theory, especially Pasteur's work and Koch's postulates.

☐ Assign questions in part B as homework.

☐ Answer questions in part A as a class; answer questions in part B in small groups.

Suggested scheduling

Average preparation time for teaching this activity = 60 minutes; average time for teaching this activity the first time = 75 minutes.

Directions for conducting the activity

Some terms used in this activity have not been defined formally; you may wish to present the following information as students need it for each part of the activity.

Antibody is a protein produced in the blood when a foreign substance or *antigen* is introduced into the body.
Pathogens are infectious agents.
Toxin is the poison produced by a pathogen. If the toxin is heated or chemically treated, it is no longer toxic, but it can still cause production of antibodies.
Toxoid (treated antigen) is the substance produced by heating or chemically treating toxins. Toxoids can cause production of antibodies, that is, they are antigenic. However, a toxoid has lost its pathogenicity.

Introduction and part A

Have the entire class read the introduction and part A and then have them study the results shown in Figure C-1. Data from a controlled experiment suggest that one animal can transfer to another something that will confer immunity to a particular disease. In this case, mice are injected with

plasma (antiserum) from a rabbit that has been immunized against diphtheria. (Note: the activity uses the term "plasma" rather than "serum." Although they are not equivalent terms, the object is to show that antibodies are transferred in the liquid portion of the blood which has been defined as "plasma" in previous activities.)

The rabbit has antibodies to the disease in its plasma. The data show that mice that are injected with the plasma from that rabbit and then are injected with diphtheria toxin do not get diphtheria. On the other hand, mice that are not protected by the rabbit plasma die after they are injected with the diphtheria toxin. These data suggest that there is something present in the blood of the immunized rabbit (antibody) that was transferred to the mice that were injected with that rabbit's plasma. That substance protected the mice against diphtheria.

For this activity, have the students work in two groups. Hand out the worksheet; have each group discuss the questions for part A on the worksheet and record their answers on this part of the worksheet. Give the students about 20 minutes to work on the questions.

Responses to worksheet questions: part A

1. (a) The rabbits had already had the disease before. That is unlikely, because diphtheria is almost always fatal. (b) The toxoid contained bacteria that were so weakened that they could not cause the rabbits to die.
2. All 25 mice in group 1 died overnight. That suggests that they died from diphtheria that was caused by the injection of the toxin.
3. Same as 2, but the mice are in group 2.
4. All 25 mice in group 2 died overnight, despite their having been given injections of plasma from a healthy rabbit prior to the injection of diphtheria toxin. That suggests that the plasma from the healthy rabbit had no protective effect against the diphtheria toxin.
5. All 25 mice in group 3 survived. That suggests that something in their treatment protected them against the diphtheria toxin. The difference in treatment between this group and the other two groups was that all mice in group 3 were first injected with plasma from the immunized rabbit and then with the diphtheria toxin.
6. The mice that were injected first with plasma from the healthy rabbit and then with diphtheria toxin died. The mice that were injected first with plasma from the immunized rabbit and then with the diphtheria toxin did not die. It appears that there is something in the plasma of the immunized rabbits that can be transferred into the mice via the plasma and that can then protect the mice from death from diphtheria.
7. No.
8. The important concept is that the data show something in the plasma that can transfer immunity, and that the something is not cells. (Plasma does not contain cells.) Remind students that plasma contains circulating proteins (refer to activity B). The proteins that help provide immunity are antibodies. The protective plasma in this experiment contained antibodies against diphtheria toxin.

Have each group present its answers to the preceding questions and, based on the answers, have the class come to a consensus on the following question (this should take no more than 5-10 minutes): Based on the observations presented to this point, what are two ways in which a person might acquire immunity against a particular disease?

1. A person can get and recover from a disease, which gives immunity against that disease thereafter. This includes having a very mild case of the disease as a result of a vaccination with a weakened pathogen.
2. A person can be given an injection of plasma (antiserum) from an animal or another person that has been immunized against the disease. The plasma includes protective antibodies.

Part B

In part B students are given data to show that immunity transferred via plasma does not explain immunity against certain diseases such as tuberculosis. Some organisms cause disease even in the presence of plasma from a person who has had that disease. The data in this part suggest that cells also play a role in the immune response.

Divide the class into two sections and have each group read part B and then consider the questions in part B of the worksheet. Allow students about 10 minutes to record their answers; have each group present its answers.

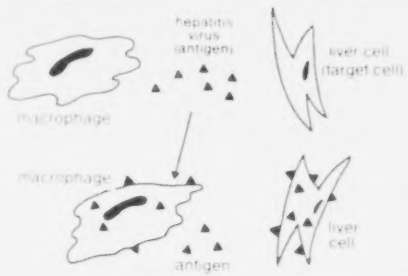
Responses to worksheet questions: part B

1. The cells that were destroying the pathogens might somehow have been programmed to recognize and destroy foreign substance—substances that are not "self." It is important for students to understand that an organism that causes disease must be recognized by the body as foreign. Otherwise, the body will not destroy that organism.
2. Jim's plasma did not contain any factor that transferred immunity from him to Joe.
3. Plasma from a person who has had this disease and therefore has immunity *will not* transfer immunity to another person. However, cells from a person who has had the disease *will* transfer immunity to another person.
4. There are at least two components of the immune system.

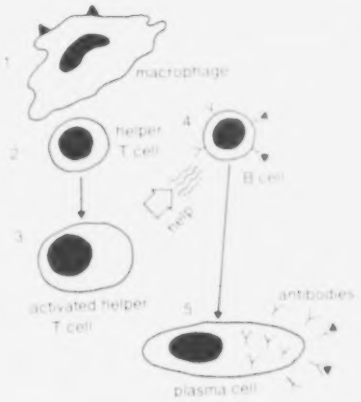
After each group has presented its answers, explain to the class that the component of the immune system that is found in plasma is known as humoral or antibody-mediated immunity, and that directed by cells is known as cell-mediated immunity. Use an overhead of the accompanying diagram (Figure C-2) to demonstrate that the two known components (antibodies and cells) of the immune system are related and to show the nature of that relationship.

Inform students that the "D" portion of the DPT shot they received as young children was diphtheria *toxoid*. It retained its antigenicity and stimulated the production of antibodies. Those antibodies will protect against exposure to *C. diphtheriae*.

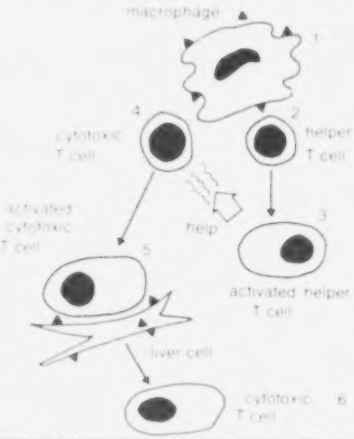
Step 1. Macrophages (scavenger cells) see invading antigens—for example, hepatitis virus—that are preparing to attack cells, in this case, liver cells. The macrophage ingests some of these viruses and pushes them back out onto its surface. Some of the virus remain free, and some invade the liver cell.



Step 2. The macrophage, which now has hepatitis virus on its surface, attracts three different kinds of T cells. These are helper T cells, cytotoxic T cells, and suppressor T cells. The macrophages that have surface antigen activate these cells. Help from the activated helper T cell, combined with the circulating antigen, activates the B cell. The activated B cell becomes a plasma cell, which produces antibodies against the hepatitis virus and destroys it. This is *humoral* or *antibody-mediated* immunity.



Step 3. At the same time step 2 is taking place, the macrophage with antigen on its surface activates helper T cells which send help to cytotoxic T cells. The combination of stimulation from the macrophage and help from the helper T cells activates the cytotoxic T cells. The activated cytotoxic T cells then destroy the target cell, in this case a liver cell which has been invaded by the hepatitis virus. After the liver cell has been destroyed, the cytotoxic T cell returns to circulation. This is *cellular-mediated* immunity.



Step 4. After the other cells have been activated, macrophages bearing the surface antigen, that is, the hepatitis virus, activate suppressor T cells. Activated suppressor T cells help put an end to the immune response, when it is no longer needed, by suppressing helper T cells. They also suppress B-cell and cytotoxic-T-cell activity, thereby stopping production of antibody and/or ending the ability of the cytotoxic T cell to destroy infected cells.

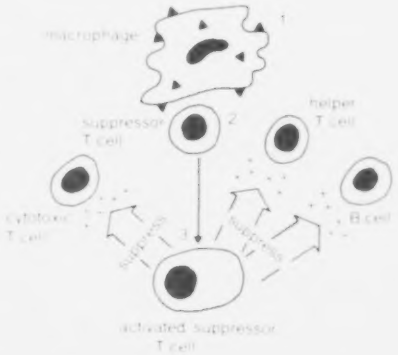


Figure C-2. Steps in the immune response. (BSCS, 1986.)

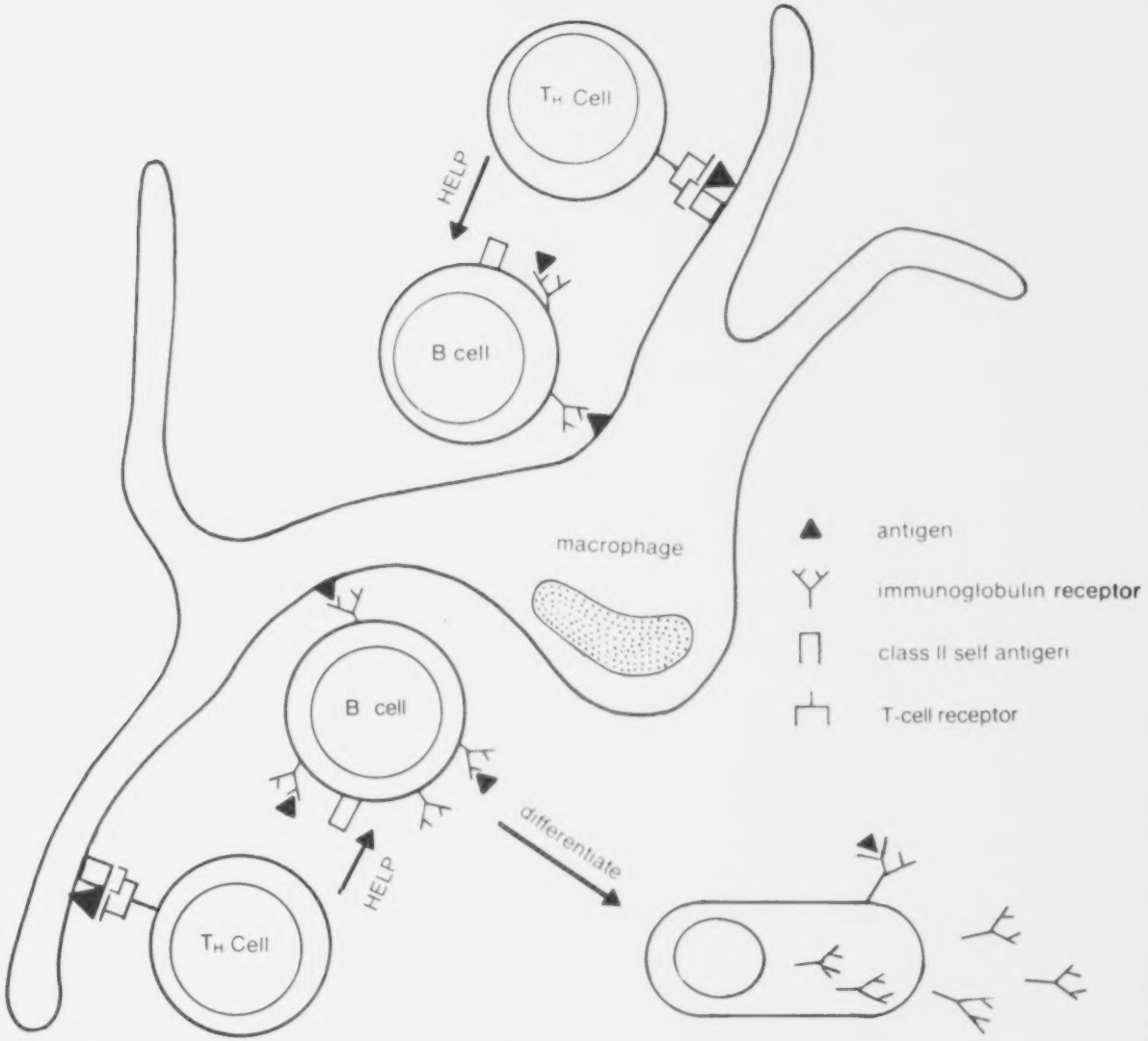


Figure 3-2. Interaction of antigen with macrophages, B cells, and helper T cells (T_H cell) leading to the production of antibody. (From Hood, et al., *Immunology*, 2nd ed., Addison-Wesley Publishing Company, 1984.)

ACTIVITY D. THE MYSTERY OF THE ALPINE SLIDE

Focus

Students are asked to develop hypotheses that explain severe allergic reaction and to describe the immune response responsible for the reaction.

Objectives

Students will have opportunities to:

1. use data to formulate hypotheses; and

2. use information from earlier activities to explain and observe an allergic reaction.

Materials and advanced preparation

None.

Relevant portions of section I

Chapter 5: Allergies and hypersensitivities. (page 19)

From the field test:
Alternative suggestions for conducting the activity

☐ Discuss the types of allergies that are common in your geographic region.

☐ Ask a local allergist to visit the class to discuss the biology and treatment of allergies.

Suggested scheduling

Average preparation time for teaching this activity = 40 minutes; average time for teaching this activity the first time = 50 minutes.

Directions for conducting the activity

Have students complete the reading. In the last paragraph, students are asked to think about the alpine slide environment. They are asked, "What factors might play a role in the apparent interaction between skin abrasion and severe allergic reactions?" You will note that the activity uses "severe allergic reaction," rather than the more technical term anaphylaxis. Some students may have heard the term; use your judgment about whether you should introduce another technical term.

Have the students stop reading at this point and ask for any ideas they may have. Record their responses on an overhead or chalkboard. Some possible factors are:

1. time of year
2. plant life surrounding the slide
3. animal life surrounding the slide
4. altitude
5. time of day
6. presence or absence of rainfall
7. temperature at time of skin abrasion
8. the asbestos on the slide
9. fear induced by the ride
10. clothing worn by the riders

You should reach no conclusion during the discussion; the goal is a list of possible factors. Now display the following data on the chalkboard or on an overhead projector.

A. Data from the alpine slide in Vermont

riders per day: approximately 1,400
rate of injury (abrasions or friction burns): 1-2% (14-18) per day
abrasions alone do not cause severe allergic reactions

B. Historical data on the occurrence of severe allergic reactions

Time Period	Rate of Allergic Reaction
23 May-27 June (1976-1981)	0 cases
28 June-4 August (1976-1981)	1.71 cases/10^5 rides
5 August-6 November (1976-1981)	0 cases

Other alpine slide operators across the United States reported 24 cases of severe allergic reactions; 22 occurred in the period from late June to early August.

Ask your students again to consider the alpine slide environment; have them look at the photograph (Figure D-1) once again. Ask: "Based on the data we have, what might be the most likely factor—from the list we have developed—involved in this problem?"

Ask a series of questions that will help students eliminate the least likely possibilities. Remind students that the data show increased occurrence during a particular time of year. Begin by eliminating those proposed causes that do not vary with the calendar. Ultimately, bring students to the realization that the occurrence of severe allergic reactions, according to the data, coincides with the grass pollination season in the mountains. Ask, for example: "Can you think of a plant process that could play a role in causing severe allergic reactions?"

Now, ask the following: "We seem to have settled on pollen as a potential explanation for those cases of severe

allergic reaction. What two, major requirements must we meet before we can state that we have demonstrated an association (*not* proof) between allergic reactions in those five young men, and pollen?"

You may have students work in groups, or conduct a class discussion of the question. Ultimately, they should see that two major factors must be demonstrated: (1) the presence of pollen grains in the area of the slide, and (2) sensitivity to pollen of that type on the part of the five patients.

These are essentially hypotheses, which can be investigated empirically. That is what the researchers did as they tried to solve this problem. Simply tell the students that factor 2 was determined by skin tests. Of the four patients tested, all were positive on the tests for grass and ragweed pollen.

Next, allow students to speculate on how one might demonstrate factor 1. There will likely be many good and creative suggestions. The researchers used glass slides coated with silicone grease and affixed to the front and rear of five sleds to collect pollen grains. More pollen grains were found on the rear slide than on the front slide. (Students can speculate the reasons for that finding.) The range was from 4 grains (front of sled, slow speed) to 1600 grains (rear of sled, high speed).

Based on the evidence presented, the most likely hypothesis is that severe allergic reactions were caused by pollen grains that were introduced into persons who are allergic to grass pollen. This occurred through breaks in the skin as a result of abrasions sustained while riding the amusement slides. Remind students that while the evidence is strong, it is still not conclusive. All other variables have not been controlled.

The researchers concluded that there is a small but recognizable risk that riders who sustain abrasions will have severe allergic reactions during the period coinciding with grass pollination at the amusement slide. Similar studies at three alpine slides in Colorado found associations between allergic reactions and the grass-pollination period.

Questions for discussion

1. Consider the symptoms listed in the activity describing severe allergic reactions: itching and inflamed skin, watery and reddened nose and eyes, difficulty in breathing. Can you think of any other human afflictions that result from allergic reactions?

   Answer: hay fever; hives; asthma; hypersensitivity to insect stings; certain types of food; penicillin or other drugs. Students will likely have some experience with one or more of these problems.

2. If you were the operator on an alpine slide and knew that skin abrasions during the grass pollination season could lead to severe allergic reactions, what steps could you take to protect your customers?

   Answer: You might post warnings of the possibility of allergic reaction at the slide to alert persons who are allergic to grass pollens; personnel at the slides could be trained in the treatment of severe allergic reactions; you might reduce the pollen in the air at the slide sites by frequent cutting, and moistening of the adjacent grassy areas. Share with students the warning prepared by the operator of an alpine slide in Utah.

ALLERGY SUFFERERS

You *may* experience a severe allergic reaction as a result of a relatively minor injury (scrape or cut) suffered on the alpine slide. Hay fever, grass pollen, and related allergy sufferers are especially at risk.

Swelling of the mouth, nose, eyes and throat, breathing difficulties, rash, itching, runny nose, and lightheadedness are all symptoms of a severe allergic reaction and need to be treated immediately.

Should you or anyone with you suffer a scrape or cut while riding the slide *and* exhibit any of the above symptoms, please contact an alpine slide employee immediately. If symptoms develop after leaving the alpine slide, contact a physician for treatment.

We suggest you continue to take your medications as directed, exercise extra caution while riding the slide (go slower, wear long pants and shirt) to reduce the extent of possible abrasions, and contact an alpine slide employee if symptoms develop.

Extensions

The mechanism involved in allergic reactions might be of interest to your students. A brief outline follows.

1. An allergy is the result of a hypersensitivity to a foreign antigen.
2. The tendency to develop some allergies is apparently inherited.
3. During an allergic reaction the offending antigen stimulates abnormal amounts of the antibody IgE.
4. The IgE antibodies combine first with the offending antigen and then attach themselves to special cells in the body known as mast cells. Mast cells are found throughout the body, but are most abundant in the dermis and in the tissues surrounding the gut, respiratory tract, and blood vessels.
5. The IgE antibodies trigger mast cells to release large amounts of histamine. Histamine causes blood vessels to dilate and fluid to leak from the circulatory system into surrounding tissues. It also stimulates the production of large amounts of mucous.
6. Antihistamine drugs relieve allergy symptoms by blocking histamine receptors on nerve endings. They do not stop histamine release by mast cells. That accounts for the delay in the effectiveness of the antihistamine drugs and for the advantage of using them before exposure.

References

Spitalny, K.C., et al., Alpine slide anaphylaxis, *The New England Journal of Medicine* 310(16):1034, 19 April 1984.

Suggested test items

Which of the following factors played the major role in the severe allergic reaction that some people had after suffering from skin abrasion injuries on alpine slides?

A. the seriousness of the skin abrasion
*B. the time of year
C. the altitude of the alpine slide
D. the air temperature at the time of the injury

What event had to occur before a severe allergic reaction could develop?

A. The reaction-causing element was transmitted by a second person.
B. The immune system had been sensitized by viruses sometime before the actual reaction took place.
C. The reaction-causing element was transmitted by a special kind of plant.
*D. There had to be breaks in the skin to allow pollen to get into the person's body.

ACTIVITY E. ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

Focus

This activity presents basic information about acquired immune deficiency syndrome (AIDS), screening for the disorder, and associated ethical, social, and psychological implications.

Objectives

Students will have opportunities to:
1. read a brief description of AIDS, including its cause and epidemiology;
2. learn how to avoid contracting AIDS;
3. understand the value of screening tests and their limitations;
4. discuss the nature of false positive and false negative results in screening tests;
5. consider which members of the population are at high risk for AIDS; and
6. discuss the pros and cons of screening for AIDS antibody.

Materials and advanced preparation

The student reading and questions for discussion are included in section III of this monograph.

You will want to discuss the reading and respond to questions about our current understanding of AIDS. Newspaper or magazine articles may be of value, but remain cautious; there is a lot of misinformation.

We suggest strongly that you read the article "AFRAIDS," which is cited at the end of the teacher materials for the activity. Many experts believe AFRAIDS, Acute Fear Regarding AIDS, is a more serious public problem for schools than is the disease itself. Education can help reduce the fear.

Relevant portions of section I

Chapter 5: Malfunctions of the Immune System (pages 19-22)

From the field test:
Alternative suggestions for conducting the activity

☐ Give a short lecture on the various types of cells in the immune system so students understand the function of helper T cells.

☐ Conduct all discussions in large groups.

☐ Invite a speaker from a local medical school or health department to discuss AIDS.

☐ Have students read and bring to class current articles on AIDS from newspapers and magazines.

☐ Use the following resources: "AIDS: Is anyone safe?," Janice H. Tanne, *Readers Digest*, February 1986; *Harvard Medical School Health Letter*. XI:1 & 2,

November 1985 & December 1985; "AIDS in the schools: A special report," *Phi Delta Kappan,* March 1986.

Suggested scheduling

Average preparation time for teaching this activity = 95 minutes; average time for teaching this activity the first time = 85 minutes.

Directions for conducting the activity

Part A

Have students complete the reading on acquired immune deficiency syndrome. This would be a good homework assignment. Discuss the reading with the class and respond to questions. Remember, however, that there are many unanswered questions about AIDS. The intent is to correct clearly inaccurate information and to dispel the myths that have already grown up around the disease.

Part B

The public policy issues surrounding the detection, control, and treatment of AIDS are quite complex and very contentious. This activity looks at only one such issue, the screening of donor blood for HTLV-III antibody.*

Discussion of screening tests performed on donated blood will help focus the activity. High risk groups (homosexual men, intravenous drug users, and hemophiliacs) may be mentioned. Screening tests for syphilis and other communicable diseases may be used as examples of tests where false positive and false negative results may occur. Have students read the section titled "Screening Donated Blood and Plasma for HTLV-III Antibody." Divide the class into groups of three to four students and give each group either questions A or questions B to discuss.

Extensions

After students have shared their ideas with the entire class, ask them how much such a testing and retesting program may cost, as well as how to go about setting up an effective notification procedure that ensures privacy. You may also want them to consider how an employer, an insurance company, or acquaintances may view a person whose test is positive for HTLV-III antibody. Who should be held responsible for possible AIDS transmission through blood or blood products? The donor? The recipient? The blood center? Should private physicians and dentists be informed of one's HTLV-III antibody status? As a summary to this activity, you may want to share recommendations and ask students whether such recommendations appear to be reasonable.

You may also want to discuss the differences between specificity and sensitivity** of a screening test. Attempt, through discussions with "A" and "B" groups, to have students come to an awareness of the following recommendations on their own, or cue them accordingly.

Recommendations

1. High risk groups should eliminate themselves as donors regardless of the use of screening tests.
2. All blood and plasma units found repeatedly to be positive for HTLV-III antibody should be removed from the distribution system.
3. Units found to be reactive on repeated testing should be tested by another method. The donor should be informed of a positive result only if it is repeatedly reactive by one type of test and also positive by another standardized method of testing.
4. Alternative test sites for HTLV-III antibody need to be established for high risk groups so that those individuals will not donate blood in order to learn their own status relative to HTLV-III antibody.

Summary

Blood recipients have a right to expect that all efforts have been made to ensure that blood they receive has been tested by the most technologically advanced methods in order to minimize the risk of transmission of infectious disease agents. At the same time, donors have a right to expect consideration and protection so that their life-giving gift does not lead to a personal disaster. How can society reach a middle ground?

The specific issue of HTLV-III screening may be resolved in time. However, students should see this as an example of the general problem of wholesale public health measures. No screening test will be perfect, whether it is for HTLV-III or cystic fibrosis. False positives and false negatives will result. In addition, human error such as mislabeling of samples will cause incorrect test results to be provided to some people. Similarly, the enormous genetic diversity in the human population ensures that some individuals will have negative reactions to broad-scale immunization (polio vaccine, for example) or to drugs (the birth control pill, for example).

*The nomenclature of the AIDS virus has been a confusing and contentious issue in the research community since the virus was first identified as the causative agent of the disease. Some refer to the virus as HTLV-III (human T-cell lymphotropic virus type III); others refer to it as LAV (lymphadenopathy virus). Participants in a special nomenclature conference held in mid 1986 suggested the designation HIV (human immunodeficiency virus). At this printing, that designation has not been adopted widely.

**Note: *Specificity* of a screening test is its ability to identify *only* the agent being sought; *sensitivity* is the ability of a test to identify that agent in *all* cases tested. Most screening tests are highly sensitive, and thus may yield false positive results.

Answers to questions for discussion

Group A

a. Screening protects the nation's blood and plasma supply from contamination.
b. Screening protects the hemophiliac from HTLV-III in blood products (factor VIII) required during bleeding episodes.
c. Screening helps ensure that the blood received does not contain the AIDS virus.
d. Possible identification of a healthy donor without symptoms of AIDS can result in medical scrutiny and early treatment should the disease occur.
e. Donors deserve privacy and protection so that if a donor unit shows a positive result for HTLV-III antibody, a personal disaster can be avoided.

Group B

a. The person who has a false negative result might, in fact, be positive. If a unit of his or her blood or plasma is used in a transfusion, there is a risk of contamination with the AIDS virus.
b. Persons identified as positive for HTLV-III antibody might face discrimination in terms of medical or life insurance, as well as in employment. In addition, there is clearly a social stigma attached to a person so identified. That person may not have the AIDS virus, nor may he or she have been exposed to it.
c. That individual's professional, social, and family life may be placed in a state of turmoil. Personal fear and depression might result for the individual who is falsely identified.
d. When the public health is at stake, concerns for the welfare of the general population have generally superseded concerns for the individual. Students will likely express varying opinions on this difficult issue. The conflict raises many complex questions about the rights of the individual and the duty to protect the public at large from harm.

Addendum

Three additional public policy issues that emerged in mid to late 1986 may interest your students:

1. The controlled study of the drug AZT (student reading, page S14) was terminated when it became clear that patients receiving the drug were improving while patients on placebo were dying. This can lead into a class discussion on the ethics of controlled clinical trials on humans.
2. The surgeon general's recommendations on "safe sex" and on sex education (student reading, page S16) stimulated much public controversy and discussion. In addition, the Institute of Medicine of the National Academy of Sciences issued a report criticizing the U.S. government for what it called underfunded and poorly coordinated efforts in research and education about AIDS. The report recommended increased funding in both areas. You may want to discuss those recommendations with your students.
3. Some experts in public health recommend that health departments in cities such as New York and San Francisco provide free, sterile needles to drug addicts to prevent the spread of the AIDS virus through shared needles. What are the pros and cons of that recommendation?

References

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AIDS: The emerging ethical dilemmas. *Hastings Center Report* 15(4), 1985.

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Osterholm, M.T., et al. Screening donated blood and plasma for HTLV-III antibody: Facing more than one crisis? *The New England Journal of Medicine* 312 (18):1185, 1985.

ACTIVITY F. THE CHEETAH--A POTENTIALLY EXTINCT SPECIES?

Focus

This activity demonstrates the interactions between genetics, immunology, and evolution.

Objectives

Students will have opportunities to:

1. investigate some factors that might contribute to the potential extinction of a species, in this case, the cheetah;
2. predict the results of experiments designed to test whether there is low genetic variation in a population;
3. explain what could happen in an immune system to account for a high degree of susceptibility to a disease in a population; and
4. decide how genetics, immunology, and evolution can interact in a population to determine the future of that population.

Materials and advanced preparation

Students should get only one part of this activity at a time. An option would be to project the student materials on an overhead. The chalkboard is a less-attractive option. Something other than a strictly verbal presentation of the student material is strongly suggested.

Relevant portions of section I

Chapter 2: Antibody diversity is genetically controlled. (page 4)
Chapter 3: T cells distinguish self from nonself. (page 11)
Histocompatibility Antigens Induce Graft Rejection (box, page 12)
Chapter 6: Diversity in the Immune Response (box, page 24)

From the field test:
Alternative suggestions for conducting the activity

☐ Provide part C from the teacher's materials for the students.

☐ Allow students to review data and answer questions in part B in small groups.

☐ Discuss other problems related to the loss of genetic diversity such as seed crops or tropical rain forests (see, for example, "Damage to Tropical Forests," *Science*, 10 October 1986).

☐ Discuss the role of skin grafts in the treatment of burn victims.

Suggested scheduling

Average preparation time for teaching this activity = 40 minutes; average time for teaching this activity the first time = 40 minutes.

Directions for conducting the activity

The format for this activity follows the procedure developed by Joseph J. Schwab, University of Chicago, and presented in his book *The Teaching of Science as Inquiry*, Harvard Press, Cambridge, MA, 1962.

The material presented to the student is incomplete. The student is asked to fill various gaps in the information. The gap may be a conclusion to be drawn from data or a hypothesis to account for the data. A good strategy is to allow students to discuss the various questions in small groups and to ask each group to present its ideas to the entire class.

You should not supply information to fill the gaps. The objectives of the activity go beyond simply learning the content. Students can discover through the kinds of problems posed, and by contributing to the solution of these problems, that science is something more than merely learning from others what others know. The students also learn that their participation often allows them to shape and improve the activities in which they are involved. Students thus develop skills in the interpretation of data and the understanding of scientific knowledge.

For a more complete discussion of the background and rationale of this kind of learning strategy, see pages 305 to 310 in the BSCS *Biology Teacher's Handbook*, 3rd edition, Macmillan, New York, 1978.

Part A

The mortality rate for cheetah populations in the wild is approximately 70 percent. (The figure is equal to the true mortality rate in the wild. The data in Figure F-1 are fictitious, and have been developed to allow students to derive the mortality rate.) Some possible student responses to the second question:

- They are the world's fastest sprinters; they are capable of speeds up to 112 km/hr for short distances.
- They have very long, slender legs and other characteristics that make this high speed possible.
- Most animals are restricted to two remaining wild populations in southern and eastern Africa.

Some possible student responses to the third question:

- There has been a reduction in their living space.
- They are killed for their pelts, which are used in fur coats and other decorative apparel.
- They are victims of some lethal infectious disease.

– They were killed by a natural disaster, such as fire or drought.

Part B

Where there is normal variation of alleles in the gene pool, one would expect rejection of the allografts. This usually occurs between 7 and 13 days after grafting. In the cheetah grafts, there was no rejection of any of the autographs or allografts, even after 75 days, when observations ended. The nonrejection of the allografts supports the hypothesis that the "population bottleneck" reduced the allelic variation in the gene pool of the cheetah.

Answers to questions in part B

1. The control is the graft from one part of a given cheetah to another part of the same cheetah (an autograft).
2. The control allows comparison of rejection patterns between the two types of grafts.
3. The rejection time for the cheetah grafts is greater than that for grafts involving humans, mice, and domestic cats.
4. The data indicate that there is less genetic variation in the cheetah population than in the human, mouse, or domestic cat populations. In fact, the researchers concluded the cheetah grafts "suggest identity of donor and recipient at the cheetah's MHC locus" (see section I, chapter 3, p. 12).
5. There is a direct relationship between the amount of genetic variation in a population and the degree of rejection of grafts from unrelated individuals.

Part C

This part of the activity can be used to assess the students' understanding of the immune system. If students can develop the steps listed below they likely have a good understanding of the system.

1. Macrophages (scavenger cells) recognize invading FIP viruses (antigens) and ingest them.
2. The ingested viruses are pushed out onto the surface of the macrophages.
3. The recognition of viruses on the surface of these macrophages activate helper T cells, which in turn activate B cells.
4. The activated B cells become plasma cells and begin to produce antibodies. This is "humoral"—or antibody-mediated—immunity.
5. Other activated helper T cells will activate cytotoxic T cells.
6. The activated cytotoxic T cells destroy any body cells that have been invaded by the FIP virus. This is cell-mediated immunity.
7. When the immune response is no longer needed, suppressor T cells are activated by the macrophages that started the whole process.
8. The activated suppressor T cells will suppress the helper T cells, the cytotoxic T cells, and the B cells. Thus, antibody production is stopped, as is the ability of the cytotoxic T cells to destroy infected cells.

During the epidemic of FIP in the Oregon colony, the above process obviously did not take place. Consequently, the FIP viruses were not inactivated or destroyed; the disease progressed within individual cheetahs and was transmitted to other cheetahs in the population. Before the FIP epidemic, the mortality rate at Wildlife Safari was approximately 25 percent, as compared to 70 percent in the wild.

Part D

Humans are often the direct cause of animal extinction because people have the ability to modify the environment. In the case of the cheetah, however, a destructive mechanism has been set into motion, and humans play no role in the process.

In the past history of the cheetah, a population bottleneck reduced the variety of alleles in the cheetah gene pool. As a result, the genetics of the cheetah population was such that all individuals were closely related. The results of the skin grafts supported this hypothesis. One consequence of this close relationship between cheetahs was that there was a great deal of genetic homogeneity (low variability) in the genes that are partly responsible for the immune response.

The immune system of the cheetah developed in a way that some foreign antigens, such as the FIP virus, were recognized as "self." Consequently, when a cheetah was invaded by these viruses the immune system did not respond and the disease was uncontrolled. Because the gene pool of the cheetah population contains very little variation, the same process took place in most of the individual cheetahs.

The cheetah population is an example of a genetically uniform species that could be wiped out by a deadly infectious disease. There would be natural selection against the population. Evolution of the cheetah species would stop, and it would become one of the many animal species that exist only in books and museums today.

References

O'Brien, S.J., et al. Genetic basis for species vulnerability in the cheetah. *Science* 227(4693):1428, 22 March 1985.

Suggested test items

Environments vary over long periods of time. What must happen to populations of organisms if they are to survive?

A. New species must frequently be created.
B. The reproductive rate must increase.
C. Such populations must cross-breed with other populations to survive.
*D. Members of the population must differ from one another for natural selection to operate.

The cheetah. (From O'Brien, S.J., et al. Genetic basis for species vulnerability in the cheetah. *Science* 227(4693):1428, 22 March 1985.)

ACTIVITY A. WHY DO SOME PEOPLE GET SICK?

Part A

Bubonic plague is a bacterial disease. It is spread to humans through the bite of fleas carried on infected animals, most often rats. The term "bubonic" derives from the swelling of lymph nodes—mostly in the groin and the armpit—that results from infection by the bacterium *Yersinia pestis,* the bacterium that causes plague. These swollen lymph nodes are called "buboes," hence "bubonic" plague. The more graphic name "Black Death" is taken from the dark appearance of the skin, which is caused by hemorrhages under the skin. These hemorrhages occur over most of the body.

Y. pestis multiplies rapidly in the lymph nodes and enters the bloodstream, which transports the bacteria to other parts of the body. If untreated, the infected person may die from pneumonia caused by severe lung infection.

The European continent first experienced local outbreaks of plague in the sixth century. Several serious outbreaks were recorded in the eleventh century. The most serious outbreak occurred in the fourteenth century, when it became known as the "Black Death." The graph in Figure A-1 shows the estimated death rate from the Black Death in fourteenth-century Europe. How many Europeans died from plague? How many Europeans survived the plague? Why do you think as many people survived as did?

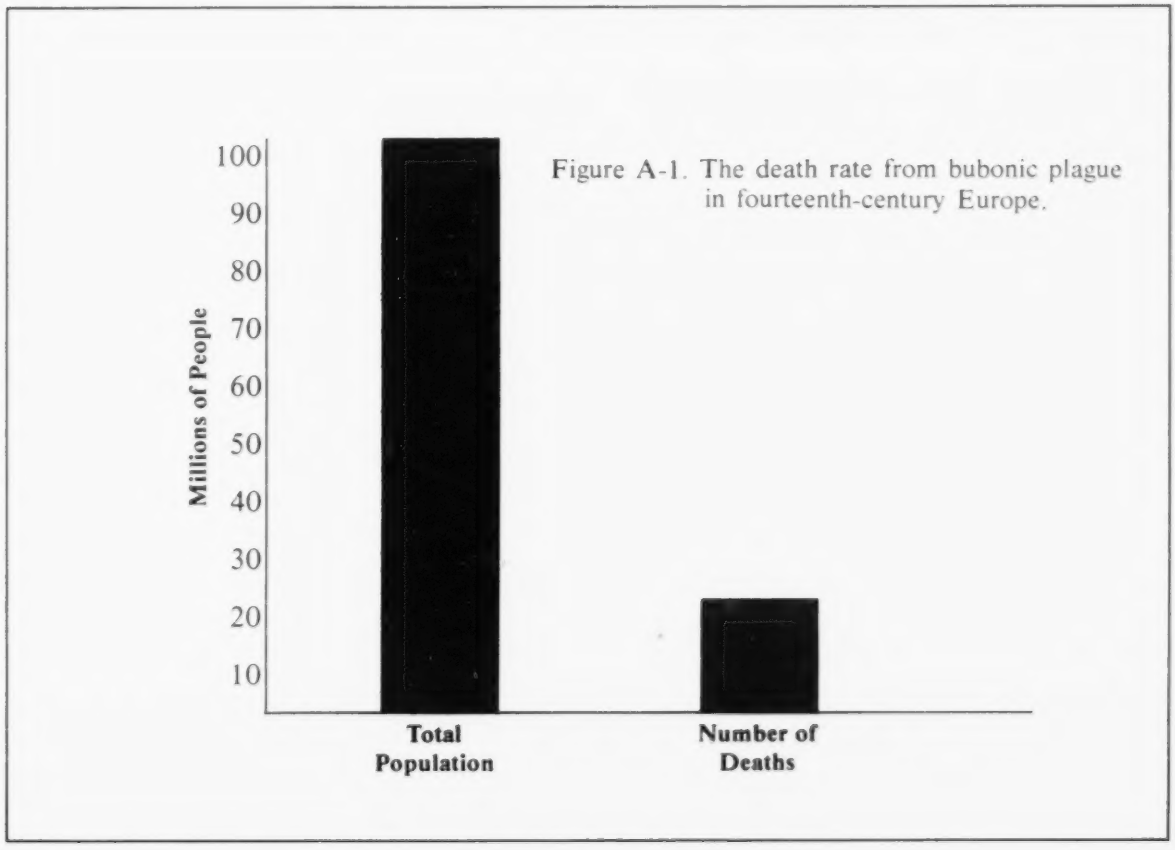


Figure A-1. The death rate from bubonic plague in fourteenth-century Europe.

Part B

The continents of Africa and Asia were also ravaged by the plague. If you look at the map of Europe, Africa, and Asia (Figure A-2), you will discover that the distribution of the disease closely follows the trade routes on those three continents. Give some possible reasons for this pattern.

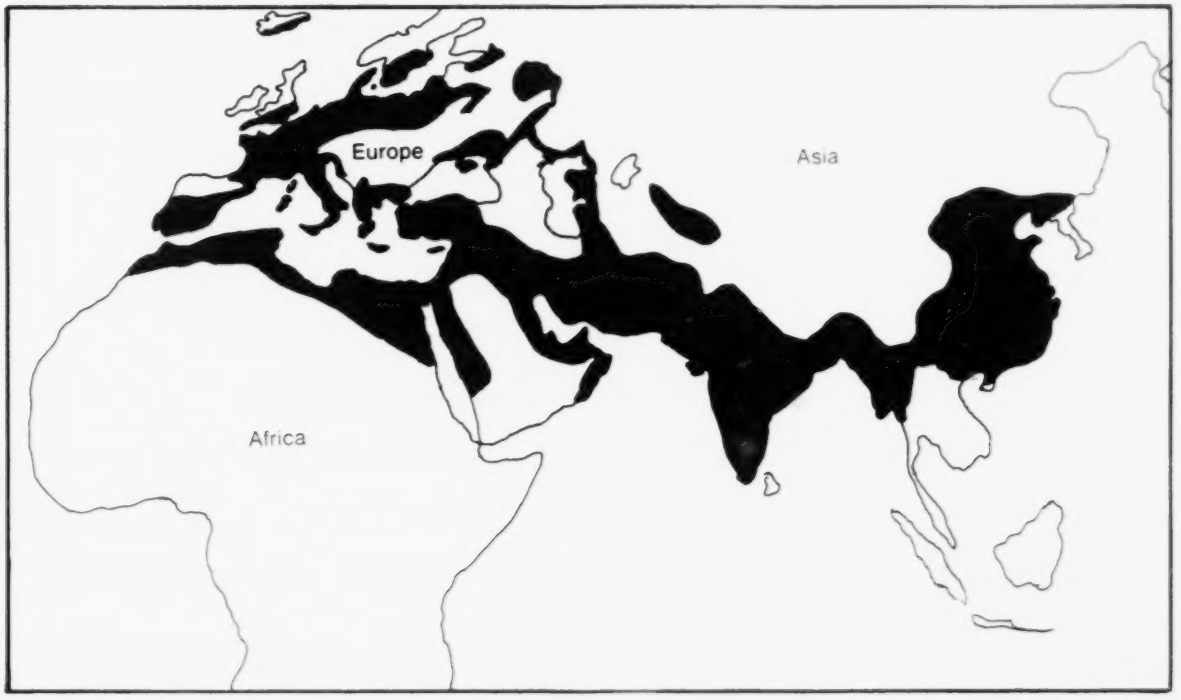


Figure A-2. Widespread occurrence of bubonic plague during the fourteenth century. (From *Science Year, The World Book Science Annual,* Field Enterprises Educational Corporation, 1968. By permission of World Book, Inc.)

Part C

Outbreaks of the plague continued throughout parts of Europe after the period of the Black Death for another 300 years. The Great Plague of London broke out in 1665. Out of a population of 460,000, approximately 70,000 people died. The long reign of plague ended in Europe after an outbreak in Constantinople in 1841.

List several factors that might have played key roles in ending the plague. Discuss how those factors played a role in ending the plague in Europe.

Part D

Another major factor in ending the plague and in the rare occurrence of it in present-day Europe is the process of natural selection. Discuss the effect of that process on the frequency of the disease.

Although plague is generally associated with the Middle Ages, there are still outbreaks today. In the United States, plague occurred in the 1800s in San Francisco, brought by ships from Asia. The disease has spread steadily eastward, and plague is now a problem along the front range of the Rocky Mountains. In 1985, there were approximately 25 cases of plague in New Mexico, and a 14-month-old girl from Colorado died from the disease.

Your teacher will provide you with additional information about modern-day outbreaks of plague. You will then be asked to propose mechanisms for controlling such outbreaks.

Part E

Now let us look at a disease that is common in the twentieth century, chicken pox. Each year, 200 to 250 thousand people, mostly young people, develop chicken pox. Fortunately for most of that large number, the disorder is relatively harmless, especially in young children. What do you know about chicken pox?

Part F

When you observed that "once you have chicken pox you will never get it again," you were defining the word "immunity." In 1665, during the Great Plague of London, not everybody who got the plague died. Those who survived the disease never developed it again. They had become immune to it, just as you did to chicken pox after having it one time. This is not true of all diseases. Think about the common cold. How many times have you had a cold? Do you have them one right after another, or is there a period of time between them? You also know that you can become immune to some diseases (such as polio) without having the disease. How is that possible? With these last few questions in mind, and thinking back over the readings and discussions, think of some questions you might have about why some people get sick while others do not.

ACTIVITY B. IDENTIFICATION OF BLOOD COMPONENTS

Human blood serves a variety of functions, and has a number of complex chemical components that allow those functions to occur. One important component will be considered in this activity.

Part A

PROCEDURE

Obtain the following materials and bring them to your work area:

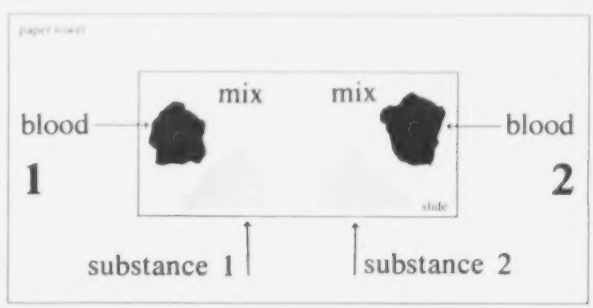
1 sterile blood-letting lancet
1 paper towel
1 alcohol prep pad
2 toothpicks
1 clean microscope slide
substances 1 and 2 readily available
*whole human blood

When you are ready to proceed, follow the directions below:

1. Place your slide on the paper towel and label the towel "1" at one end of the slide, and "2" at the other end, as in Figure B-1.
*2. Carefully cleanse one of your middle fingers with the alcohol prep pad and allow the alcohol to dry. (If you do not wish to draw your own blood, use the whole human blood that your teacher has available for you.)
3. Puncture your finger with the sterile lancet and wipe away the first drop of blood with the alcohol pad. Caution: never use the same lancet more than once. Gently squeeze your finger and place one drop of blood at one end of the slide labeled 1, and a drop at the other end of the slide labeled 2. Gently press the alcohol pad against your finger; the bleeding should stop soon, if it has not already.
4. Obtain the vial labeled substance 1 and place a drop of that next to the drop of blood labeled 1. Place a drop of substance 2 next to the drop of blood labeled 2.

Use a toothpick to mix substance 1 with the blood. Do the same with substance 2, **using a different toothpick**. Try to avoid spreading the mixture of blood and substance too much, as that may cause the blood to dry too rapidly. Take care to prevent mixing substance 1 with substance 2 as you combine those components with the blood.

Figure B-1. Position slide in the middle of paper towel.



RESULTS AND INTERPRETATIONS

1. Observe the two mixtures of blood and substance. What do you see happening? Check with two or three of your classmates and notice whether they have similar or different reactions. Record what you see in your notebook.
2. Your teacher will collect all the data and record the results on the board. Reactions with blood and substance 1 will be recorded, as well as reactions with blood and substance 2. Any other combinations of reactions or absence of visible reactions will also be recorded.
3. In small groups of three students each, consider the following:

    a. What seems to be happening (or not happening) when blood is mixed with one of the two substances?
    b. Devise three hypotheses (more, if possible) that might explain how blood and the substances cause the type of reaction you have observed.
    c. If substance 1 caused a reaction with the blood with which it was mixed, would that type of reaction be desirable in a transfusion? Why or why not?
    d. From the data recorded on the board (which you may want to copy), formulate a statement that might account for the observations that sometimes blood will react with substance 1 but not 2, or that blood will react with substance 2 and not 1, or other combinations noted from the data. Consult Figures B-2 and B-3 to help you formulate your statements.

Discuss your group's hypotheses and interpretations with your teacher. A member from each group should share that group's ideas with the entire class.

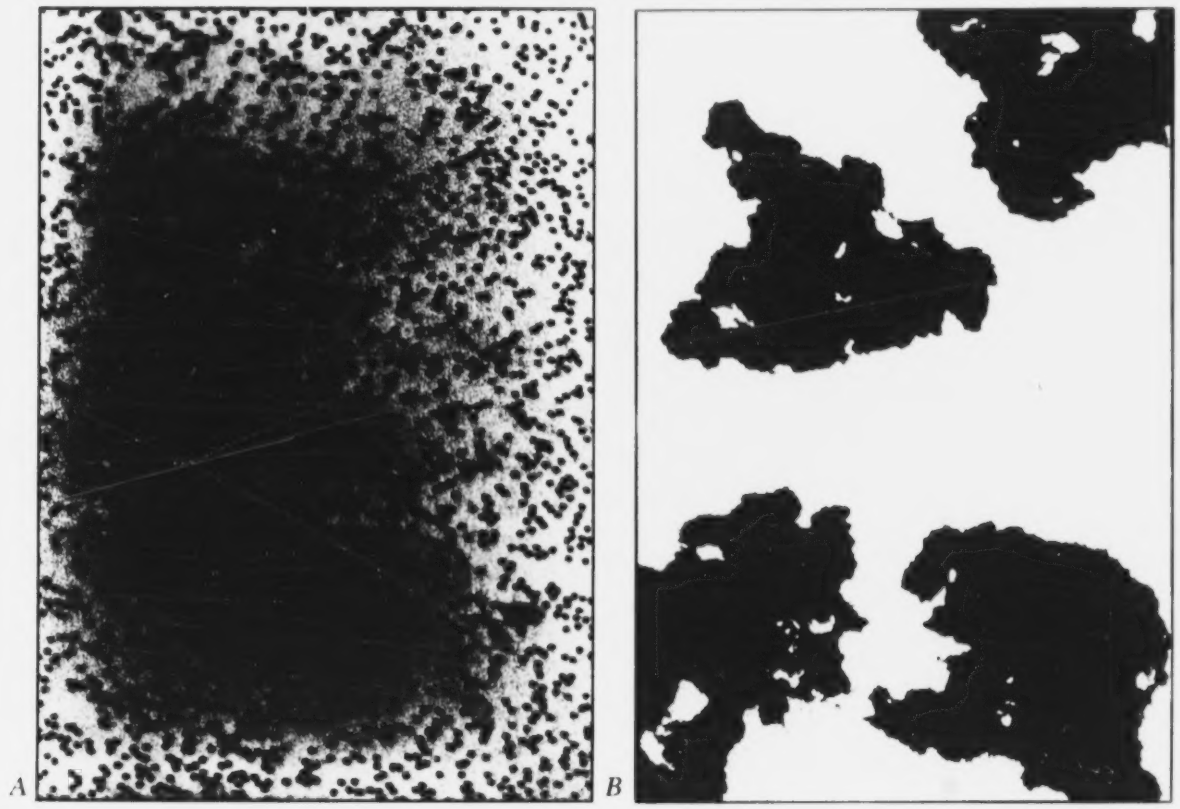
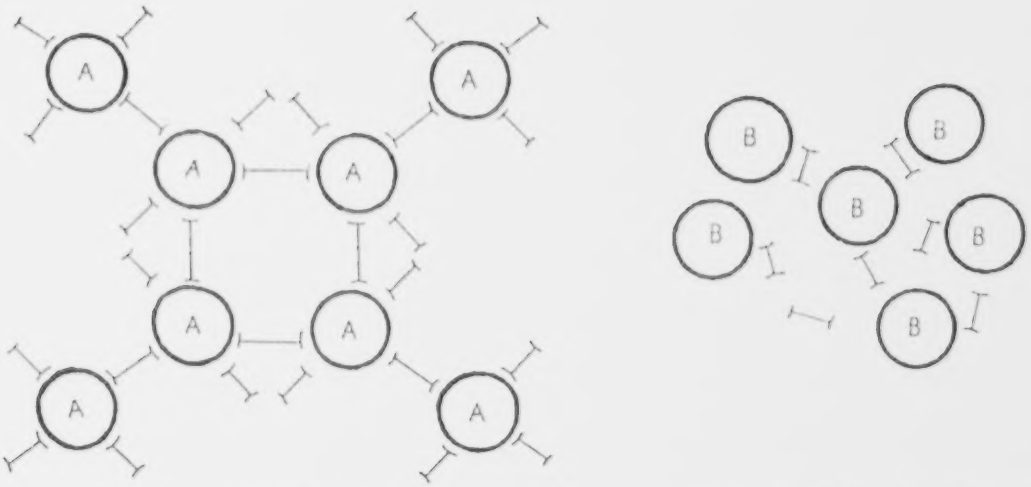


Figure B-2. Human red blood cells before (A) and after (B) adding plasma containing anti-A antibodies. The agglutination reaction indicates the presence of the A-antigen on the surface of the cells. (From *Introduction to Immunology,* John W. Kimball, Macmillan Publishing Company, Inc., 1983.)



Clumping or Agglutination of Red Blood Cells Type A by Anti-A Antibody

No Agglutination of Red Blood Cell Type B by Anti-A Antibody

Figure B-3. ABO Typing. (From *Immunology: Its Role in Disease and Health,* Immunology Task Force Report, 1980. Courtesy National Institutes of Health.)

Part B

A LIFE ON STANDBY*

Their suitcases are always packed as 11-year-old Tommy and his parents wait for a phone call. That phone call will make the difference between life and death for Tommy. The family awaits word from Children's Hospital that a donor has been found for a liver transplant—an operation that Tommy needs to save his life. The family has been told that the call will likely come within the next three months, and the parents will have less than six hours to get Tommy to the hospital. Local companies have volunteered the use of their aircraft to fly Tommy and his parents to the hospital. Plans for a special charter flight have also been made in the event that those planes are not available when the call comes.

Tommy's parents discovered their son's affliction when he was only two weeks old and doctors became concerned about the yellow tone of his skin. Tommy was born without bile ducts; he had his first operation before he was three months old. He has undergone 12 operations and has been hospitalized about 60 times. He was near death several times. Of course, when the transplant operation does occur, the physicians will have to work hard to keep Tommy's body from rejecting the donated liver.

Although Tommy is afraid that he is going to die, his mother says that her son's attitude is "terrific." He still enjoys the pastimes of other children his age, and passes the school vacation time by fishing, bicycle riding, and playing with his friends—and waiting for that important phone call.

*Adapted from the article "Lakewood boy, 10 on 'standby' status for liver transplant," *The Denver Post,* 16 July 1985.

The only symptoms that show Tommy is dealing with a life-and-death struggle are his yellowed eyes, and a pouch he must wear on his side. Doctors have decided to do the liver transplant now as Tommy faces a growth spurt that his liver may not be able to withstand.

Tommy's medical expenses thus far have exceeded one million dollars. The liver transplant operation could cost as much as $300,000. The family's medical insurance does not begin to cover all of those bills. About $7,000 has been raised through local fund-raising activities, and contributions are still being sought to help pay for an operation needed to save the life of a young boy.

QUESTIONS FOR DISCUSSION

1. Why must Tommy wait so long for an operation that is so desperately needed?
2. When the phone call finally does come, what further problems or complications might occur as a result of the operation?
3. How might Tommy's physicians increase the chances that the transplanted liver will "take"?
4. Is there any danger to Tommy in using treatments following the transplant that will help to ensure success of the graft?
5. Should organs from nonhuman donors, such as a heart from a baboon, be used for humans?
6. The cost of transplant surgery and the preparation for such operations is exceedingly high. Most medical insurance plans do not provide coverage, because the insurers claim that transplant surgery is still in the "experimental stage." Discuss that issue with members of your group.
7. There are many more people in need of donated organs than there are organs available. That situation often raises difficult dilemmas about who is to have first access to organs that become available.

   Assume, for example, that only one liver becomes available for the following three people: (a) a wealthy man, age 68; (b) a poor, single mother of three young children—she is 34 years old; (c) a third-year medical student—she is 25 years old. All are equally well matched for the donated liver. Discuss with your group the following questions:

   a. What criteria should be used to decide who gets the donated liver?
   b. What are the two most important criteria? Why did you choose those?
   c. What does your selection of those two criteria tell you and others about your values?
   d. Based on your criteria, who should get the donated liver?
   e. Who should be responsible for making such decisions?

ACTIVITY C. WHAT PROVIDES IMMUNITY?

In this activity you will investigate some theories about the human immune system. The activity includes readings and points for discussion and asks you to make observations from data.

Introduction

For many years, scientists did not understand why only those people who had recovered from the plague could safely care for the ill (see activity A, "Why Do Some People Get Sick?").

Part A

The germ theory of disease, developed in the late 1800s, proposed that microorganisms cause disease. The idea that a specific organism could cause a specific disease enabled scientists to propose hypotheses about prevention and treatment. One hypothesis, for example, was that killing or weakening the organism would enable an infected person to recover. Research also led to questions about how the body resists or overcomes infection. Consider the following experiment:

Diphtheria is a bacterial disease that attacks the upper respiratory system, the nose, throat, and tonsils. The disease is caused by the bacterium *Corynebacterium diphtheriae.* The bacteria produce a *toxin* that destroys nerve cells and eventually causes heart failure. A toxin is a poison produced by a disease-causing organism. The toxin produced by *C. diphtheriae* is more deadly than cobra venom. Diphtheria can be fatal if not treated promptly. It is especially serious in young children.

Scientists heated this toxin to cause the destruction of its poisonous properties. The resulting substance is called diphtheria *toxoid.* Toxoid was injected into two rabbits. Two weeks later, blood samples were collected from the rabbits, the cells were removed, and the plasma—the liquid portion of the blood—was saved. The following experiment was then carried out with three groups of mice.

Group 1. Twenty-five mice were injected with diphtheria toxin.

Group 2. Twenty-five mice were injected with plasma from a healthy rabbit. Ten minutes later they were injected with diphtheria toxin.

Group 3. Twenty-five mice were injected with the plasma saved from the two rabbits that had been injected with diphtheria toxoid. Ten minutes later those mice were injected with diphtheria toxin.

Figure C-1 shows what the scientists observed on the following day. Consider the questions in part A on the worksheet. Record your answers on the worksheet.

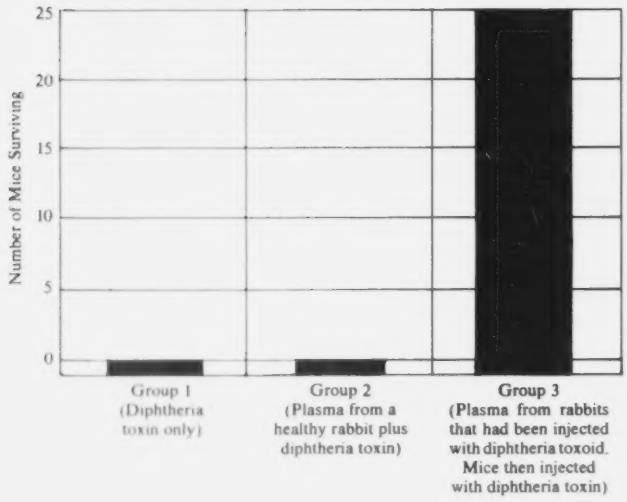

Number of Mice Surviving
25
20
15
10
5
0
Group 1 (Diphtheria toxin only)
Group 2 (Plasma from a healthy rabbit plus diphtheria toxin)
Group 3 (Plasma from rabbits that had been injected with diphtheria toxoid. Mice then injected with diphtheria toxin)

Figure C-1. The survival of three separate groups of mice. Group one was injected with diphtheria toxin. Group two was injected with plasma from a healthy rabbit and then with diphtheria toxin. Group three was injected first with plasma from rabbits injected with diphtheria toxoid. The mice in group three were then injected with diphtheria toxin. (BSCS, 1986.)

Worksheet: Part A

1. Provide two possible explanations for the fact that the injected rabbits did not die from diphtheria.

2. What are possible explanations for the deaths of the mice in group 1?

3. What are possible explanations for the deaths of the mice in group 2?

4. What do the deaths of the mice in group 2 suggest about normal rabbit plasma?

5. How can you explain the lack of illness in the mice in group 3?

6. The experimenter used plasma taken from the rabbit that was injected with the diphtheria toxoid, and plasma from the normal rabbit. What is different about the two plasmas, based on the data?

7. Does plasma contain cells?

8. What could be in plasma that could transfer immunity to a disease from one animal to another?

Part B

The mouse experiment provides only part of the answer to the nature of the immune response. After reading the following information, respond to the questions in part B on the worksheet below. Record your answers on the worksheet.

Elie Metchnikoff, a Russian zoologist, noted that when certain pathogens—infectious agents—are introduced into the blood of animals or humans, specialized cells quickly engulf and destroy the invaders.

Jim Smith, a 15-year-old, is exposed to and contracts tuberculosis, which is caused by the bacterium *Mycobacterium tuberculosis.* His brother, Joe, is given an injection of plasma from Jim's blood. Although the injection is given at the proper time, Joe still gets the disease.

A baby, Chris, is born without a thymus gland, which is responsible for the development of certain white blood cells. Chris develops a serious rash that is caused by a common fungus. Most people have had this disease and have experienced only very mild symptoms. But this baby's life is soon in danger as a result of the infection. Chris' mother had the same disease, so some of her plasma is transferred to Chris. The disease becomes more serious. In an attempt to save Chris' life, the doctor transfers some of the mother's white blood cells to the baby, and the baby recovers from the disease.

Worksheet: Part B

1. What might cause the cells that Metchnikoff observed to destroy the pathogens?

2. Explain how Joe got tuberculosis even after he was injected with plasma from Jim.

3. What can you conclude about the nature of the body's immune defense against the fungus that caused Chris' disease?

4. Based on the mouse experiment and on the data from Jim, Joe, and Chris, what can you conclude about the number of components in the immune system?

ACTIVITY D. THE MYSTERY OF THE ALPINE SLIDE

During the two-week period from 22 July-8 August 1982, five young men vacationing in Vermont experienced severe allergic reactions. Certain areas of their skin displayed slightly raised patches that were inflamed and produced rather severe itching. They had hay-fever-like symptoms in the nose and eyes. They had some difficulty breathing and their blood pressure was in the low range.

The doctors who treated the five recognized from their symptoms that they were reacting in a highly sensitive manner to the presence of some foreign substance in their bodies. They were quickly treated with injections of antihistamines and epinephrine, drugs that prevent the production of the agents that cause the reactions. All five men recovered.

The doctors were puzzled by these medical events. In checking out their patients they found all five shared a common experience. All their allergic reactions occurred within a three- to 20-minute period after each one of the five had sustained some skin abrasion injuries while riding on an amusement device called an alpine slide (Figure D-1). These slides are common in ski areas, where they are built on the ski runs. They generate income for the ski areas during the spring, summer, and fall.

The slide consists of a free-running sled that glides down a mountainside on an asbestos-cement track. The abrasion injuries occurred as a result of falling off sleds that were running the alpine slide course.

A check of 27 similar alpine slides in the United States revealed 24 similar cases of severe allergic reactions, 22 of which followed skin abrasions. So, evidence seemed to indicate a relationship between allergic reactions and skin abrasions while riding on an alpine slide.

The doctors knew that skin abrasions by themselves do not bring about severe allergic reaction. Something more must be involved. Put yourself in the place of the medical team investigating this problem. Think about the environment of the alpine slide. What factors might play a role in the apparent interaction between skin abrasion and severe allergic reactions? Discuss the possible environmental factors with your teacher and the rest of the class. Your teacher will then pose some additional questions.

Figure D-1. An alpine slide. (Courtesy of Broadmoor Alpine Slide.)

ACTIVITY E. ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

Part A

Read the following article about acquired immune deficiency syndrome. Your teacher will provide additional information and will respond to your questions. Remember, however, that there is a great deal that is still unknown about AIDS.

WHAT IS AIDS?

AIDS is a disease of the immune system that is usually acquired after birth by people who previously had perfectly normal immune responses. Other immune deficiency diseases are either acquired during the development of the fetus, or last only a short time, usually following an illness. AIDS is caused by a virus that invades and destroys cells of the immune system. By the fall of 1986 approximately 26,000 people had been diagnosed as having AIDS. The Centers for Disease Control estimates that the number could rise to 270,000 by 1991.

How does this virus cause AIDS? There are very few viruses that can invade cells of the immune system, and most of them are cancer-causing viruses. Interestingly, although there is no evidence that the AIDS virus actually causes cancer, it is a close relative of viruses that can cause leukemia—one type of cancer. The AIDS virus enters a cell of the immune system, where it multiplies and eventually kills the cell, releasing other viruses that invade more of the same kind of cells.

This virus will not invade all cells of the immune system, but prefers a certain kind of cell, called a helper T cell. The role of helper T cells is to help other cells of the immune system do their jobs. Without that help, the other cells function very poorly.

AIDS results from the destruction of helper T cells. The patient, therefore, becomes highly susceptible to many kinds of infections and tumors. Indeed, the hallmark of AIDS is the presence of parasitic, fungal, and viral diseases. In addition, there is an increase in a number of different kinds of cancer, most commonly a type of cancer called Kaposi's sarcoma, which is actually very rare. The AIDS virus does not cause the disease directly; the disease AIDS is the result of massive infections by many types of organisms because the immune response to them does not occur.

HOW DO YOU GET AIDS?

In order to get AIDS, the virus must, of course, be introduced into the body. Most commonly, that occurs through sexual contact between homosexuals. The virus has been found in the semen of infected males. Nearly 75 percent of all cases as of late 1986 occurred in homosexual and bisexual males. We do not know why the disease in this country began among homosexual males; there are other viral diseases, such as hepatitis, that are more common among homosexuals than in the general population. Bisexual males, who become infected originally because of homosexual contacts, have transmitted the disease to their female sexual partners. There have been a few cases of transmission from infected females to male sexual partners.

Most of the remaining infected individuals (about 17 percent) are drug addicts who use intravenous injections and share needles. If one individual has the virus in his or her blood, another person using that same hypodermic needle can inject the virus into his or her own blood, and subsequently develop the disease. (You cannot acquire the infection from an injection given to you by a doctor or other health professional because **all** of the needles they use are used once and then destroyed. There is no way they can be contaminated by another person's blood, even in a blood bank.) The remaining AIDS cases are hemophiliacs and other recipients of multiple blood transfusions, and babies born to infected mothers. Because the virus can cross the placenta, an infected mother can transmit the virus, and hence the disease, to her unborn baby.

MISCONCEPTIONS

There are many common misconceptions about AIDS and how it is transmitted. Although the virus has been detected in low amounts in the saliva of some infected people, there is no evidence as yet that it can be transmitted effectively through saliva. A person sneezing or chewing on a pencil or spitting in the water fountain will not be able to transmit the virus effectively. The virus cannot be transmitted on toilet seats or through towels. You will not get it from the swimming pool or from the locker-room floor.

AIDS is **not** transmitted through casual contact, even in a family setting. The only family members of an AIDS patient who have contracted the disease have done so by sexual contact or blood transfusion, or else have contracted the disease *in utero,* before birth. Of the thousands of doctors, nurses, orderlies, and other hospital personnel who work with AIDS patients, few have gotten the disease, and those who have were either homosexuals (or bisexuals), recipients of multiple blood transfusions, or sexual partners of AIDS patients. Only one health care worker is reported to have contracted the disease from an AIDS patient. That resulted from a needlestick injury and exposure to the blood of the patient.

PROSPECTS FOR TREATMENT

Why can we not treat AIDS effectively? Maybe we will be able to, and maybe soon. However, there are two important things to remember about AIDS. First, it is caused by a virus. Today, we have only a few drugs that can control or prevent any viral infections.

There is hope, however. The genes of the AIDS virus are made up of RNA instead of DNA. In order to multiply, the virus must make DNA from its RNA. It must then replicate its DNA, and make a new RNA. Human and other animal cells cannot make DNA from RNA; they can only do the opposite, that is, make RNA from DNA. Viruses whose genes are made of RNA have an enzyme that allows them to accomplish this tricky biochemical feat. Animal cells lack this enzyme. If a drug could be found to inhibit this enzyme, and no other, then it should be able to prevent the AIDS virus from replicating without harming the infected cell.

There are some drugs that can do this, at least in the test tube. A drug developed in mid 1986, AZT, attaches to the enzyme—reverse transcriptase—in test tubes. AZT reduces the number of infections AIDS patients get and prolongs survival for a few months. There are some severe side effects from the drug, and it is still experimental. Researchers are not sure that AZT works in the body the same way it works in the test tube. Studies are still in progress.

Another reason that AIDS is difficult to treat is that the disease only occurs after the helper T cells have been destroyed. Even if we had a drug that could kill the virus, it might be too late to save an AIDS patient; it takes a long time to regenerate the immune system, and the patient may die of other infections before then. Many of the infections that AIDS patients get cannot be treated by any of the drugs we have today.

Can we develop a vaccine to prevent AIDS? Yes, but it will take some time. There is a tremendous amount of research being done to develop an AIDS vaccine, and there are some promising results from animal experiments. However, it will take several years to develop a vaccine that can be used safely in humans. A vaccine always carries a risk, and the worst situation would be for the vaccine itself to cause AIDS. Other side effects could occur, and the relative risks and benefits would have to be evaluated for this vaccine just as they are for any other.

AIDS AND BLOOD DONORS

What about AIDS from a blood transfusion? Only a small fraction of AIDS patients contract the disease from a blood transfusion. Today, all potential blood donors are questioned closely about their life-styles, and people belonging to the high risk groups, mainly homosexuals (and bisexuals) and intravenous drug users, are not allowed to donate blood. We all know, however, that not everyone tells the truth all the time. Blood banks now screen all donated blood with a very sensitive test to detect the presence of antibodies against the AIDS virus. Blood found to be positive by this test is destroyed. Thus, the likelihood of contracting AIDS by blood transfusions, always remote, has now become highly improbable.

MANY QUESTIONS REMAIN

Will AIDS become a serious venereal disease in the general, heterosexual population—something like genital herpes or gonorrhea? It might. The AIDS virus can clearly be transmitted by heterosexual contact. It is a good idea to be certain that your sexual partner has not been exposed to the AIDS virus.

Can AIDS be transmitted by kissing? The evidence suggests that this is not likely, but some experts feel that prolonged "deep kissing" (tongue kissing) might be sufficient to transmit the virus. In general, the AIDS branch of the Centers for Disease Control states: "Heterosexual transmission . . . appeared to be most closely associated with being a steady heterosexual partner of a person with AIDS or of a seropositive individual (person who has AIDS antibody) in a risk group."

AIDS will remain a serious problem among homosexuals (and bisexuals) and intravenous drug users for a long time. It is already a major cause of death among males 25-44 years of age in Manhattan and San Francisco. We do not know how long a person has to have the virus before he or she develops symptoms of the disease, but the evidence indicates that it is probably several years. There will be many more cases among heterosexuals and among recipients of blood transfusions who became infected before the disease was identified. Evidence suggests that many people who have no symptoms may carry and transmit the virus. We do not know whether all of those people will eventually develop AIDS, or whether some of them will continue to have the virus and not the disease.

There are many questions about AIDS that have not yet been answered. Where did this very virulent virus come from? (It appears to have arisen in Africa, perhaps among monkeys.) How did it become a human disease? Was it sudden? How did it reach the United States? Will everybody who becomes infected with the virus get the disease? Do people who develop AIDS already have a mild immunodeficiency that makes them susceptible to this more serious disease? Is the likelihood of developing the disease related to the number of AIDS viruses infecting the individual? In nearly all other diseases, the probability of developing the disease is directly related to the number of organisms infecting the person.

Even though there are many unanswered questions about AIDS, researchers at the Centers for Disease Control feel confident in making the following recommendations about prevention:

> To be safe from risk of exposure to HTLV-III infection, persons should avoid any sexual activity that involves the exchange of body fluids, such as semen, with an individual who is known or suspected to be infected.
>
> For uninfected individuals likely to continue sexual exposure to HTLV-III, such preventive measures as condoms, diaphragms, or spermicides offer some theoretical protection, but their efficacy is unproved.
>
> The Public Health Service has recommended that women with . . . evidence of infection with HTLV-III should postpone or avoid pregnancy to prevent transmission to the fetus or newborn. Women who may have been exposed should have a blood test for HTLV-III before considering pregnancy. Premarital and prenatal screening for antibody to HTLV-III should be seriously considered by physicians or clinics providing care for women in populations with increased risk of infection, such as intravenous drug users.
>
> In addition, donors of organs, tissue, or sperm should be serologically tested for HTLV-III to prevent transmission. (From *Science* 229(4720):1352, 1985.)

In October 1986 the surgeon general of the United States, Dr. C. Everett Koop, issued a report to the American people about AIDS. He stressed the seriousness of the AIDS epidemic for the entire population, not only the high risk groups. He recommended that all people begin to practice "safe sex," that is, the use of condoms and a limitation on the number of sexual partners. Dr. Koop also recommended that sex education classes begin as early as third grade to continue through high school as part of the battle against AIDS.

The rise of AIDS as a major public health problem raises many questions about public policy. There are no easy answers to such questions. Public education is essential so that important decisions are not based on misinformation, fear, and prejudice. You will discuss the implications of one AIDS-related policy decision in part B of this activity.

Some other questions for you to think about include:

> Should a child with AIDS be allowed to attend school with other children? Why or why not?

The brother of your best friend has AIDS. Should you stop visiting your friend? Why?

Can you get AIDS by donating blood? Why?

Which do you think is more important, finding a drug to cure AIDS or developing a vaccine to prevent AIDS? Why?

Part B AIDS and Public Policy: Screening Donated Blood and Plasma for HTLV-III Antibody

AIDS infection has been associated with several well-defined high risk groups, including recipients of blood and blood products. The disease is thought to be caused by a virus called human T-cell lymphotropic virus type III (HTLV-III). Screening blood for contamination by HTLV-III, therefore, has become one of the highest public health priorities and is currently used nationwide.

The test detects HTLV-III *antibody* in the blood. This means that the person has been exposed to the HTLV-III virus. It does not necessarily mean that the person has AIDS or even that he or she will develop AIDS at a later date. It does mean, however, that the donated blood from that person should not be transfused into other individuals.

Despite the use of the screening test to identify HTLV-III antibody, each year thousands of volunteer blood donors will be falsely identified as positive for HTLV-III antibody if screening tests for blood and plasma are used. False positive results indicate that a person **has** the HTLV-III antibody when in fact the person **does not** have the antibody in his or her blood. Evaluation of screening tests must always include the probability of error. For example, the tests may be done improperly or samples may be mislabeled. Adverse publicity and personal trauma may result for a donor who receives a false positive report from a blood donation. Many experts worry that there will be a marked decrease in the pool of volunteer blood donors in conjunction with widespread concern about the AIDS epidemic. That decrease in the donor pool could result in life-threatening shortages of blood and plasma.

In addition to screening donor blood for HTLV-III antibody, health experts recommend that members of high risk groups voluntarily refrain from donating. Many experts believe that is necessary to reduce the possibility of blood contamination by the HTLV-III virus.

For the person who is truly positive for HTLV-III antibody, notification and elimination from the donor pool is indeed appropriate. However, for donors falsely labeled as antibody positive, those results may do needless harm to their social and personal relationships.

DIRECTIONS

Your teacher will divide the class into groups of three or four students. Your group will discuss the following questions from either group A or group B. Record the results of the discussion in your group, and report those results to the class.

QUESTIONS FOR DISCUSSION

Group A: Provide arguments **for** the nationwide screening program for HTLV-III antibody in blood banks. As you do so, you might wish to consider the following questions:

a. Of what value is the screening program for the general public?

b. How do hemophiliacs, who may require frequent blood cell products (factor VIII) benefit?

c. Of what value is this screening to blood recipients in general?

d. Of what value is screening to a healthy donor infected with HTLV-III?

e. What rights do blood donors have?

Group B: Provide arguments **against** the nationwide screening program for HTLV-III antibody in blood banks. As you do so, you might wish to consider the following questions:

a. What problems might arise from a false negative result from screening for HTLV-III antibody?

b. What problems might arise from a false positive result?
Consider employment or medical insurance.

c. How might a positive test for HTLV-III antibody affect the life of that individual?

d. In the use of screening tests, there is concern both for the public at large and for the individual. What kinds of conflicts might arise as a result of those concerns?
How might society reach some compromise?

ACTIVITY F. THE CHEETAH—A POTENTIALLY EXTINCT SPECIES?

Part A

The Convention of International Trade in Endangered Species lists more than 1,000 animal species as being threatened by extinction. That seems like a large number. Biologists investigating this problem, however, estimate that, of the five to 10 million living biological species, as many as one million species will become extinct by the year 2000. That is equal to losing one species each hour from now until the end of this century.

There are 37 species in the cat family (Felidae). All except the domestic cat are considered endangered. One cat, the cheetah, is of particular concern to zoologists. The cheetah usually avoids family groups. Because of its solitary nature, estimates of its population vary widely (from 1,000 to 25,000 animals). Whatever the actual figure, it is low, and a source of concern. In addition, cheetah cubs appear to suffer from a high mortality rate. Figure F-1 shows the mortality data for cheetah cubs born in Kenya in a one-year period. What is the mortality rate (in percent) in this population?

What do you know about the cheetah? Can you think of any reasons why the cheetah population is so low and in danger of extinction?

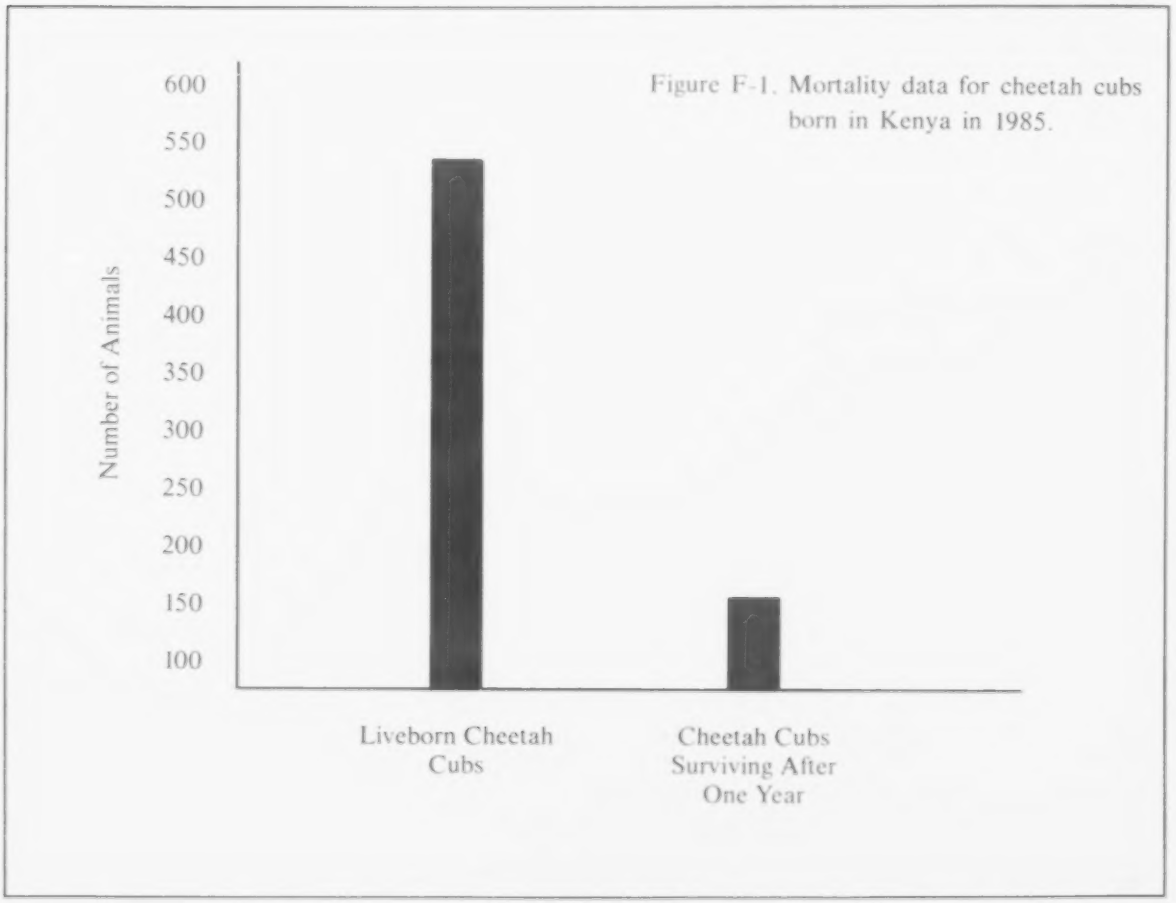


Figure F-1. Mortality data for cheetah cubs born in Kenya in 1985.

Part B

One factor that is thought to contribute to the small population of cheetahs is a "population bottleneck." Some time in its recent evolutionary history, something caused the number of cheetahs to become very small. Whatever the cause, an infectious disease or a natural catastrophe such as a fire, for example, the result was a reduction in the variety of alleles in its gene pool.

Researchers conducted the following experiment to determine the amount of genetic variation in the cheetah population: Skin grafts were made between six pairs of unrelated cheetahs. Grafts from one part of the animal to another part of the same animal also were done on all 12 of the cheetahs. Examine the data in Figure F-2, which show the results of skin grafts in humans, mice, and domestic cats. Compare those data to the data on the cheetah grafts shown in Figure F-3.

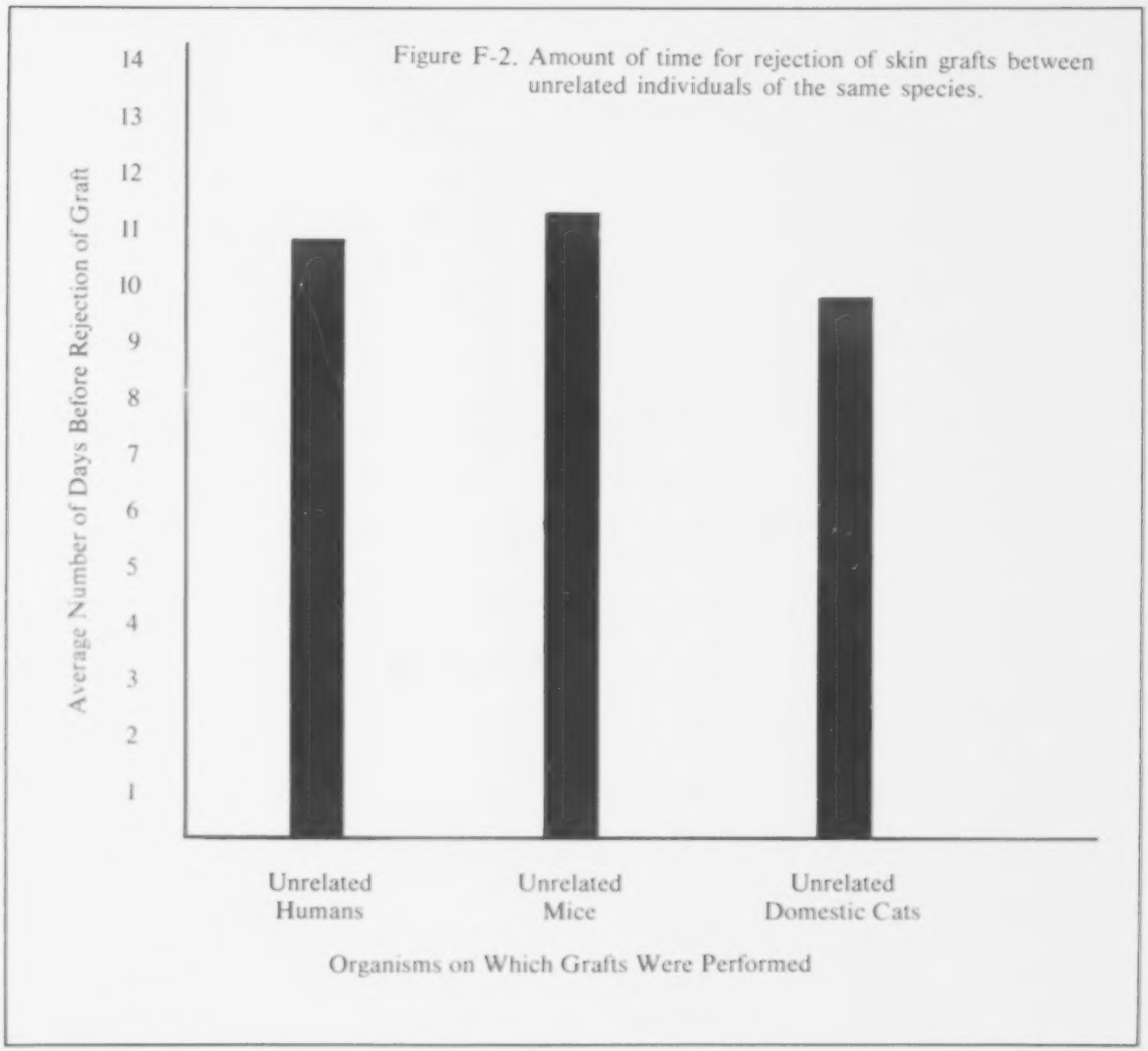
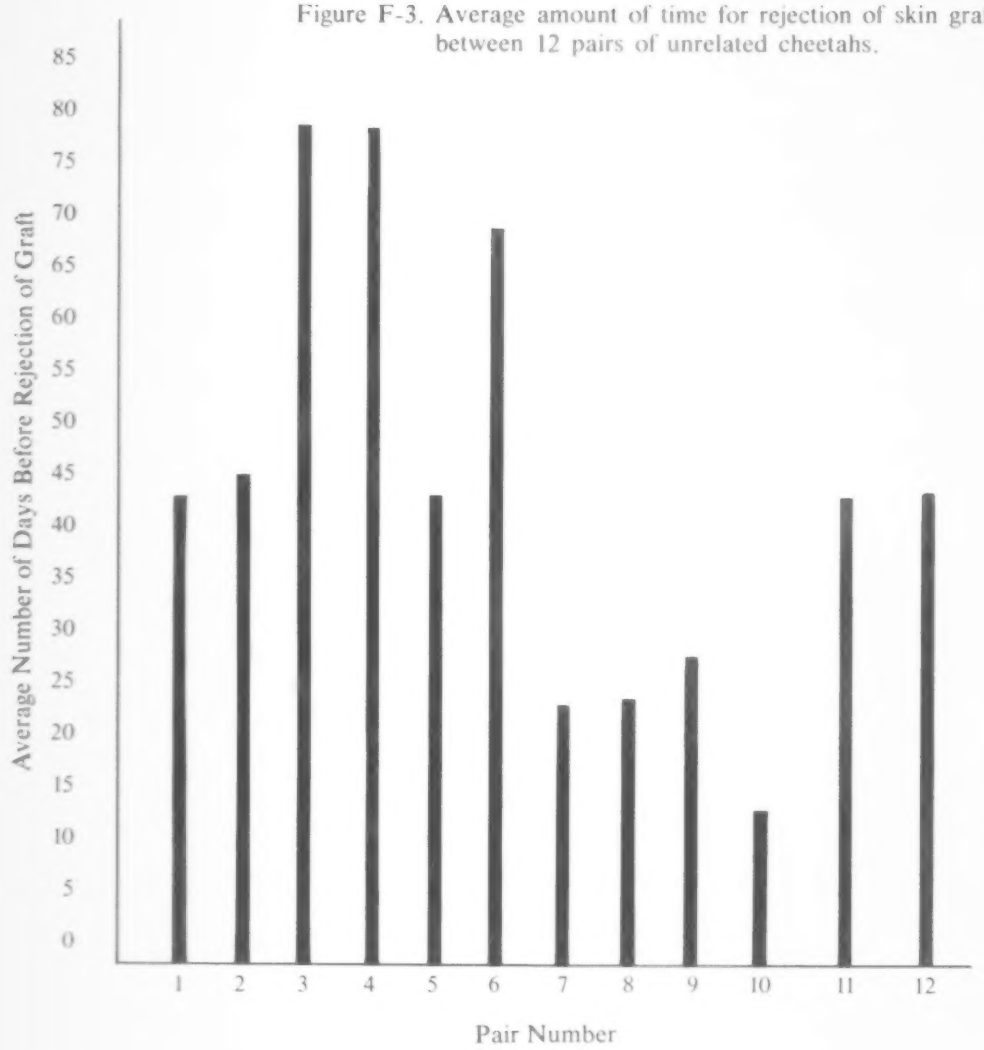


Figure F-2. Amount of time for rejection of skin grafts between unrelated individuals of the same species.

Figure F-3. Average amount of time for rejection of skin grafts between 12 pairs of unrelated cheetahs.



There was no rejection of the grafts made from one part of an animal to another part of the same animal. Write your answers to the following questions on a separate sheet of paper:

1. Which graft is the control in the cheetah experiment?

2. What does it control for?

3. Is the rejection time for the cheetah grafts greater than or less than the rejection time for the grafts shown in Figure F-2?

4. Based on these data, and on what you know about the rejection of transplants, is there more or less genetic variation in the cheetah population than in human, mice, or cat populations?

5. What is the relationship between the amount of genetic variation in a population and the degree of rejection of grafts from unrelated individuals?

Part C

When there is evidence that an animal population is declining in the wild, as is the cheetah population, breeding programs are started in zoological parks and wildlife preserves. Many large mammals such as the Pere David's deer, the Mongolian wild horse, and the European bison are extinct in the wild and survive today only because of these managed breeding programs.

One of the most successful breeding programs for the cheetah is at Wildlife Safari in Winston, Oregon. Since 1973, 73 offspring have been born from 18 litters. Figure F-4 shows the mortality data for this population. Compute the mortality rate (in percent). Compare that mortality rate to the one in the wild, presented in part A of this activity. How much better is it?

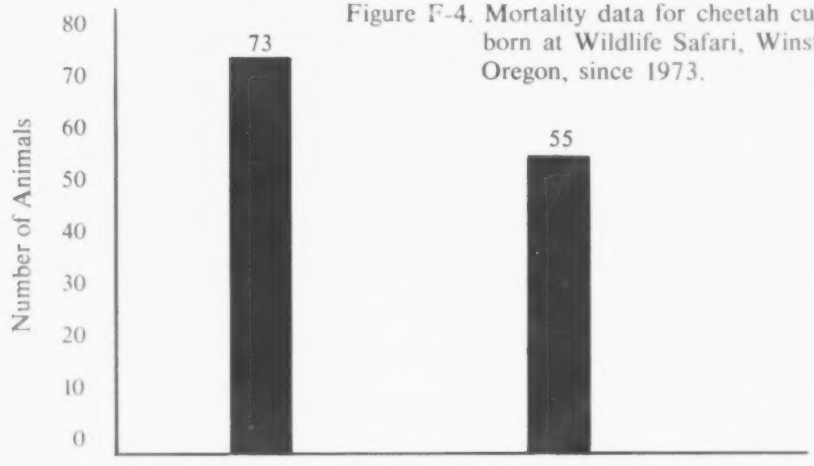


Figure F-4. Mortality data for cheetah cubs born at Wildlife Safari, Winston, Oregon, since 1973.

Part D

In May 1982 at Wildlife Safari, a healthy, eight-year-old female developed feline infectious peritonitis (FIP); she died within one week. From that date to the end of 1983, 90 percent of the cheetah population developed symptoms of FIP; despite treatment, 18 cheetahs died.

Obviously, there was an epidemic of FIP in the cheetah population in Oregon. The biologists studying the cheetahs asked the following questions: Is there any correlation between the lack of genetic variation among the cheetahs and the incidence of the disease FIP?

Parts of the immune system recognize "self" components; the body will not form antibodies against those components. Researchers, therefore, hypothesized that the immune system did not recognize the FIP virus. The genetics of the cheetah, for some reason, identified the virus as "self" and developed no immunity to the virus. This problem would occur only in an extremely small number of individuals in animal populations that have a normal amount of genetic variation. Only this small number would develop FIP. In the cheetah population, where the genetic variation was very low, many of the cheetahs recognized the virus as "self." The result was a devastating occurrence of FIP.

Discuss the relationship between genetics, immunology, and evolution as demonstrated by this story of the cheetah.

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